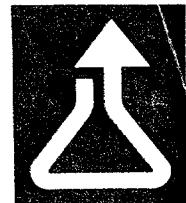


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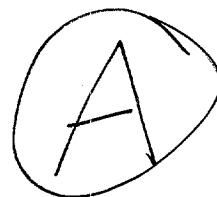
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Washington, DC 20460

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INIT



Dear Sir or Madam:

Re: 8(e) CAP-0103; Data Submission

The enclosed document is submitted pursuant to the TSCA Section 8(e) Compliance Audit Program and the CAP Agreement between Rohm and Haas Company and the Environmental Protection Agency. This document does not contain confidential business information.

The following is a summary of the contents of the submission under Unit II.C.3 of the CAP Agreement:

Tested Chemical:	Compound BX-2475, 2-Propenamide, N,N'-methylenebis-110-26-9
CASRN:	
Title of Report or Study:	A Subchronic (13 Week) Evaluation of the Potential Neurotoxicity of Intraperitoneally Injected Compound BX-2475, Compound BX-2487 and a Mixture of These Two Compounds (BX-2326) in the Albino Rat (Report No. 80RN-1019)
Reportable Effect:	Clinical and histopathological evidence of neurotoxicity (Doses: 2.5, 10, 50 mg/kg).

If additional information is required, please contact the undersigned at (215) 592-3139.
Thank you.

Sincerely,

Ronald L. Keener, Ph.D.
Regulatory Affairs Director
Product Integrity Department

RLK:so
Enclosure

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80RN-1019

RESEARCH REPORT

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E.H. & L
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A SUBCHRONIC (13 WEEK) EVALUATION
OF THE POTENTIAL NEUROTOXICITY OF
INTRAPERITONEALLY INJECTED COM-
POUND BX-2475, COMPOUND BX-2487 AND
A MIXTURE OF THESE TWO COMPOUNDS
(BX- 2326) IN THE ALBINO RAT

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original

by:

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S. Yong, B.Sc., M.Sc.

C. Bier, Ph.D.

U. DeBonis, Ph.D.

B.G. Procter, D.V.M., M.Sc.

For: Nalco Chemical Company
2901 Butterfield Road
Oakbrook, IL 60521

Project No. 9088

Date: October 2, 1980

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RESEARCH REPORT

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A SUBCHRONIC (13 WEEK) EVALUATION
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W

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BIO-RESEARCH LABORATORIES LTD.

A SUBCHRONIC (13 WEEK) EVALUATION OF THE
POTENTIAL NEUROTOXICITY OF INTRAPERITONEALLY
INJECTED COMPOUND BX-2475, COMPOUND BX-2487 AND A MIXTURE OF
THESE TWO COMPOUNDS (BX-2326) IN THE ALBINO RAT

This research was conducted at Bio-Research Laboratories over the period January 21 - August 25, 1980, under the direction and approval of:

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Study Director

Date

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SUMMARY

PAGE 001

Seven groups of five male and five female Fischer 344 rats were dosed daily, five days a week, by intraperitoneal injection with test article solution BX-2475, BX-2487 or BX 2326 for a total of thirteen weeks. Acrylamide served as the control article. Dosing commenced on January 21, 1980 and concluded on April 18, 1980. Study ended on April 21/80.

There were no deaths during the study. Dose related symptoms such as salivation, lacrimation, hunch-back position, *tip-toe walking, body tremors, piloerection and weakening of hind legs were observed among animals which were treated with the highest dosage (50 mg/kg) of BX-2475 and [BX-2487]. Some but not all of these clinical manifestations suggestive of neurotoxicity were also seen among those animals receiving either 10 mg/kg of BX-2475 or 2.5 mg/kg of BX-2487. The toxicity of BX-2326 appeared minimal, only a few incidence of lacrimation being seen.

Treatment with the highest dosage of BX-2475 (50 mg/kg) profoundly restricted the animals' growth. This was evident by the fact that these animals had the lowest body weight and smallest body weight gains throughout the study. Female rats in this group even registered an overall weight loss during the treatment period. The highest dosage of BX-2487 also had a negative impact on animals' growth. However, the magnitude of reduction was not as great as that seen among BX-2475 treated rats (50 mg/kg). The single dose level of BX-2326 (50 mg/kg) did not seem to have any effect on the rate of growth when compared with the remaining groups.

Food consumption measurement in this study, in general, revealed little adverse effect when values for control animals were compared with those receiving BX-2475 at either 2.5 or 10 mg/kg or BX-2487 at 2.5 mg/kg. Those rats receiving 50 mg/kg of these two compounds ate considerably less food. Males but not females receiving BX-2326 at 50 mg/kg showed a slight decrease in appetite.

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Macroscopic examination at necropsy showed an overall poor condition in the female rats. There was a tendency for the animals' coats to be very loose and in those females which had received BX-2475 at 50 mg/kg, emaciation was obvious. No other abnormalities were seen.

Histopathological examination by light microscopy indicated that all treated animals including Acrylamide controls sustained varying degrees of peripheral nerve damage. The lesions were characterized by ovoid and giant oxonal swelling, myelin disintegration, myelin corrugation, ovoid and tomaculum formation. The extensiveness of the damage appeared to be compound-related rather than strictly dose-related for both male and female rats. The damage effected by BX-2326 at a dose level of 50 mg/kg seemed more pronounced than that of control article, Acrylamide (at 10 mg/kg). The degenerative changes of peripheral nerve tissues induced by BX-2487 and BX-2475, however, were less severe than that produced by Acrylamide. Nerve fibers in the medulla oblongata, on the other hand, showed little change whether treated with either test article or the Acrylamide control.

INTRODUCTION

This study was undertaken to evaluate the potential neurotoxicity of compounds identified as BX-2475, BX-2487 and BX-2326. Acrylamide was used as the control article. The test/control articles were dissolved in sterile water before being intraperitoneally injected into the appropriate animal once daily, five days a week for a period of thirteen weeks. Dosing commenced on January 21, 1980 and concluded on April 18, 1980.

This study was designed to meet the requirements of the Food and Drug Administration and was conducted in compliance with the "Good Laboratory Practices" published in the Federal Register, December 22, 1978.

MATERIALS AND PROCEDURESAnimals

Forty (40) male and 40 female "Fischer 344" rats, 7 weeks of age, were received from Charles River Breeding Laboratories, Wilmington, Mass. on January 3, 1980. Upon arrival at Bio-Research Laboratories Ltd., all animals were examined by a veterinary aide to ensure their "normal" health status and were found to be in satisfactory condition. Thirty-five animals of each sex were randomly assigned to seven experimental groups using a computer based pseudo-random number generating system. The remaining ten rats (5 of each sex) were subsequently discarded. At the commencement of dosing, body weights of male rats ranged between 155 and 221 g, and females 109 to 151 g.

Animal Management

During the study, the animals were permanently identified with ear notches and individually housed in stainless steel wire mesh cages of conventional design. Each cage was fitted with an automatic watering device. The animal room was environmentally and photo period controlled (temperature $21^{\circ}\text{C} \pm 2^{\circ}\text{C}$, humidity 50% $\pm 10\%$, 12 hours light and 12 hours dark).

Animals were given ad libitum a standard commercial certified rodent diet (Purina Rodent Laboratory Chow 5002) and fresh municipal tap water. Details of analysis of the diet and water used are given in Appendices 1 and 2.

An acclimation period of two weeks allowed animals to become familiar with the laboratory setting before dosing was initiated.

Test and Control Articles

Supplies of 500 gm of BX-2475 (a fine white crystalline substance), 1 quart of BX-2487 (a clear colorless liquid) and 4 quarts of BX-2326 were delivered to Bio-Research Laboratories Ltd. on October 18, 1979 from Field System Department, Nalco Chemical Company. Three 100 g bottles of the control article, (Acrylamide) also a white crystalline substance, Code No. 11382, Batch No. 32428A, were received on January 18, 1980 from ICN K&K Labs of Plainview, N.Y. All test and control articles were stored at room temperature throughout the study.

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Experimental Design

The seven groups of ten animals (5/sex/group) were identified and treated according to the following experimental design:

<u>Group No.</u>	<u>Treatment (Dose Level)</u>	<u>Rat No.</u>	
		<u>Males</u>	<u>Females</u>
I	Acrylamide Control 10 mg/kg	101-105	151-155
II	^{ACRYLIC ACID} Compound BX-2475, 2.5 mg/kg	201-205	251-255
III	Compound BX-2475, 10 mg/kg	301-305	351-355
IV	Compound BX-2475, 50 mg/kg	401-405	451-455
V	^{2 HET A} Compound BX-2487, 2.5 mg/kg	501-505	551-555
VI	^{2 HET A} Compound BX-2487, 50 mg/kg	601-605	651-655
VII	^{2 HET A} Compound BX-2326, 50 mg/kg METHYLENE GS-ALK.	701-705	751-755

The dose levels were provided by the sponsor. Fischer 344 rats were chosen for the study since this species has been used most for studying the neurotoxicity of acrylamide and its related compounds.

Treatment

The animals were treated daily, five days a week. Individual doses were calculated according to each animal's body weight which was recorded thrice weekly during weeks 1 - 3 and weekly thereafter. A constant dose volume of 0.133 mL/100 g body weight was used throughout the study. Test/control solutions were prepared fresh daily. The appropriate concentrations for each test/control solution were achieved by serial dilution:

<u>Group No.</u>	<u>Treatment (Dose Level)</u>	<u>Concentration of Test/control Solutions Prepared</u>
I	Acrylamide Control 10 mg/kg	0.75%
II	Compound BX-2475, 2.5 mg/kg	0.1875%
III	Compound BX-2475, 10 mg/kg	0.75%
IV	Compound BX-2475, 50 mg/kg	3.75%
V	Compound BX-2487, 2.5 mg/kg	0.1875%
VI	Compound BX-2487, 50 mg/kg	3.75%
VII	Compound BX-2326, 50 mg/kg	3.75%

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All test/control articles were dissolved in sterile water for injection. 10 mL samples of each test/control article solution were sent to the Quality Control Department of Bio-Research Laboratories Ltd. for analytical testing on January 21, February 25 and April 7, 1980. Results of these analyses as well as the analytical procedures used are given in Appendix 3. The results indicate, overall, a high degree of accuracy in preparation of test/control article solutions.

Clinical Examination

Each animal was subjected to a twice daily examination (a.m. and p.m.) for any ill health or compound related symptoms, especially symptoms indicative of neurotoxicity.

Body Weight

The animals' body weights were recorded weekly in the acclimation period, three times a week during the first three weeks of treatment and thereafter once weekly.

Food Consumption

The food consumption of individual rats was recorded weekly.

Terminal Studies

On the day of necropsy, two rats/sex from the Acrylamide control group and 3 rats/sex from the test article treated groups were weighed, anesthetized with ether and perfused through the heart with 4% phosphate-buffered paraformaldehyde solution for one minute, followed by 5% phosphate-buffered glutaraldehyde continuously circulating for ten additional minutes. Animals were then subjected to a gross examination and sections from the medulla oblongata, from the sciatic nerve at mid-thigh and from branches of the distal tibial nerve were washed in phosphate buffer and post-fixed in 2% Dalton's chrome osmium.*

* Tilson, H. and Cabe, P., Acrylamide Neurotoxicity in Rats: "A Correlated Neurobehavioural and Pathological Study".
Neurotoxicology 1:89-104 (1979)

Thereafter, epon blocks containing samples of each of these three nervous tissues were prepared. They were then sent to Dr. U. DeBoni of the University of Toronto who subsequently prepared 1 um sections of each tissue and thereafter undertook their histopathological evaluation using normal light microscopy.

For the remaining rats in each group, a similar macroscopic examination was performed after which the same nervous tissues were removed and placed directly into 4% buffered formalin and retained until further notice.

Archives

All data, slides, tissues, etc., generated and recorded during the study, together with samples of test/control articles used, protocols and final report are stored in the scientific archives of Bio-Research Laboratories Ltd.

RESULTS

Bio-Research's Time Notation System is explained in Table 1. Dosing commenced on January 21, 1980 and concluded on April 18, 1980.

Mortality

No deaths occurred during treatment.

Clinical Signs

An incidence table which categorizes the observed indications of neurointoxication, is presented in Tables 2 & 3 for males and females respectively. Symptoms were seen mainly in high dose groups being particularly prominent in rats receiving BX-2475 at 50 mg/kg. Superficial wounds, alopecia, rough hairs and dry skin were observed among all groups but these findings were not considered treatment related. Clinical signs for control and treated animals can be summarized as follows:

a) Acrylamide (Control)

No obvious signs of neurointoxication were noted at the given dose level (10 mg/kg). Female animals No. 153 and 154 were found to be hyperactive on treatment day 5.2. Only one case of lacrimation was reported in this group.

b) BX-2475

Animals receiving 2.5 mg/kg exhibited no apparent signs of neurotoxicity. One female rat (No. 254) showed intermittent congestion during the seventh week of treatment and onwards.

Some animals receiving 10 mg/kg were noted to have nasal discharge and congestion. Male rat No. 305 showed piloerection once.

Clinical signs, indicative of neurotoxicity, such as salivation, lacrimation, piloerection, body tremor, fast respiration, hunched back position, tip-toe walking, and in severe cases, staggering were frequently observed in animals

receiving 50 mg/kg. Some of these symptoms were seen as early as the first week of treatment. The general condition of these animals became very poor as the study progressed. Urine stains around the lower abdominal region and subsequently alopecia on the ventral surface were also observed. The grip strength in some animals' hind legs appeared to be decreased.

c) BX-2487

Dark stains or discharge around eyes and nares, occasional lacrimation and body tremors were noted in low dose (2.5 mg/kg) animals.

In high dose (50 mg/kg) animals, shortly after dosing and lasting up to 3 hours, salivation was seen from week 2 onwards. Noticeable lacrimation, starting at approximately the same time post-treatment was observed from week 6 onward. Urine stains around the lower abdominal region were also common in this group. Sporadic hunched back position, tip-toe walking and piloerection were also demonstrated by some animals in this group. These symptoms were less intense and of shorter duration than those observed in animals receiving BX-2475 at 50 mg/kg.

d) BX-2326

Sporadic lacrimation, occurring shortly after dosing, was the only significant symptom noted.

Body Weights

Group mean (\pm S.D.) body weights and mean body weight gains (\pm S.D.) are presented in Tables 4 and 5 for males and females respectively.

Individual body weight data for male and female rats in this study are listed in Appendices 4 and 5.

Animal growth curves are plotted in Figures 1 and 2.

a) Acrylamide

This substance, as stated earlier, was used as a control in the present study. The body weight growth in these animals is thus used as a reference. However, it should be stated that at the onset of their treatment with acrylamide at 10 mg/kg, the females showed a body weight loss after which recovery occurred over weeks 2 - 7. A body weight loss during weeks 7 - 9 was rapidly recouped thereafter. The body weight of the male rats appeared unaffected by treatment.

b) BX-2475

Apart from minor, transient reductions in the female body weights at the onset of dosing, animals receiving 2.5 or 10 mg/kg of this compound showed no adverse body weight changes during the study.

At the high dose level (50 mg/kg), however, both males and females showed an initial body weight loss at the onset of dosing followed by gradual recovery and a very poor rate of body weight gain thereafter (as compared to all of the remaining groups of animals on the study). Although the body weights of the high dose females were lower than those of the remaining groups at the onset of dosing (Fig. 2), the effect of treatment with BX-2475 at 50 mg/kg is still obvious.

c) BX-2487

At 2.5 mg/kg, there were no adverse body weight changes observed during the study.

At 50 mg/kg, only male rats showed any treatment related body weight changes. In these animals, the rate of body weight gain was slightly reduced during the first two weeks of dosing and a clear body weight loss occurred in week 3. Thereafter, their growth pattern tended to be similar to that of the controls.

d) BX-2326

Treatment with this compound at 50 mg/kg produced no adverse effects on the body weights of females while in the males, minor body weight losses occurred during dose weeks 1 and 2. However, it is considered overall that the male rats' body

Since the animals were fasted overnight prior to sacrifice, the terminal body weights recorded show, in all groups, obvious body weight loss during week 13. This is, of course, unrelated to treatment. Overall group mean body weight gains were therefore calculated over weeks 0 - 12 and found to be as follows:

<u>Group No.</u>	<u>Compound</u>	<u>(Dose Level)</u>	Body Weight Gain (g) Weeks 0 - 12	
			<u>Males</u>	<u>Females</u>
I	Acrylamide	10 mg/kg	95.2	26.6
II	BX-2475	2.5 mg/kg	96.4	27.2
III	BX-2475	10 mg/kg	97.4	22.8
IV	BX-2475	50 mg/kg	28.0	5.6
V	BX-2487	2.5 mg/kg	106.4	33.4
VI	BX-2487	50 mg/kg	69.6	31.0
VII	BX-2326	50 mg/kg	83.4	30.8

The values clearly indicate the poor weight gain in rats receiving BX-2475 at 50 mg/kg and in males receiving BX-2487 at 50 mg/kg and the slightly lower weight gain in males receiving BX-2326 at 50 mg/kg.

Food Consumption

Group mean absolute food consumption (g/rat/day) throughout the study is presented numerically in Tables 6 and 7 and graphically (g/rat/day) in Figures 3 and 4. Individual values for the same period are recorded in Appendices 6 - 7. For completeness sake, group mean relative food consumption (g/rat/day) during the study is presented in Tables 8 and 9 while individual values over the same time interval are presented in Appendices 8 and 9.

a) Acrylamide

Food consumption in these "control" animals decreased following the onset of dosing and this reduction tended to persist throughout the study (minor improvements occurring only occasionally). This effect was obvious in females as can be seen by comparison of Figures 3 and 4.

b) BX-2475

Rats receiving 2.5 or 10 mg/kg showed a pattern of food intake similar to that of the controls while those receiving 50 mg/kg showed a much greater reduction in food intake during the treatment period.

c) BX-2487

At 2.5 mg/kg, the food intake pattern was similar to that of the controls while at 50 mg/kg the animals showed a reduction in food intake similar to that of rats receiving BX-2475 at 50 mg/kg, i.e. marked reduction in food intake. However, in these animals, the effect tended to be greater in the males.

d) BX-2326

Reduced food intake during the treatment period followed a pattern similar to that of the controls with the exception that in males, the reduction was greater during the final 6 weeks of treatment.

Gross Pathology

Macroscopic examination at the termination of the study showed female animals generally to be in poor condition and those receiving BX-2475 at 50 mg/kg were emaciated. Their hair coat was rough and loose and came off easily during handling. No other abnormalities were seen.

Histopathological Examination

Light microscopic examination was undertaken by Dr. U. DeBonis of the University of Toronto and his report is presented on pages 15 to 23.

Histopathological examination revealed that animals from all groups (I to VII inclusive) sustained a moderate to severe peripheral nerve damage. The degenerative changes included fiber loss, folded or corrugated myelin, myelin disintegration, tomaculum and ovoid formation, as well as oxonal swelling. However, fibers in the medulla oblongata of the same animals showed only minor changes or no changes at all.

ME 0023

The extent and severity of the nerve degeneration did not seem to be strictly dose-related since the changes observed in high dose animals were less than those seen in rats receiving lower dosage of the same test article (e.g. Group II > Group III, and Group V > Group VI). Furthermore, males and females were affected similarly by the test or control articles.

The pathologist concluded that the damage caused by BX-2326 (50 mg/kg/day) was greater than that of the Acrylamide control (10 mg/kg/day) but BX-2487 and BX-2475 respectively were less damaging when compared with the control article.

Errors and Omissions

The only dosing error committed during treatment was that female rat No. 253 was injected with 0.21 ml of BX-2475 (2.5 mg/kg) solution instead of 0.20 ml of the same test solution during dosing period 10.1 - 10.5.

Due to the balance failure and technical error, food consumption of Group VI and VII animals during study periods 5.1 - 6.1 and 10.1 - 11.1 respectively were not recorded.

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CONCLUSION

- 1) There were no deaths recorded during the study.
- 2) Test articles BX-2475 and BX-2487, administered daily, five days a week, by intraperitoneal injection at a dose level of 50 mg/kg to Fischer 344 rats appeared to be toxic to rats of both sexes.
- 3) Clinical signs indicative of neurotoxicity were evidenced by salivation, lacrimation, piloerection, body tremor, hunched back, tip-toe walking and in some cases, weakening of hind legs.
- 4) Female animals, in general, tended to have poor coat condition by the time treatment was completed.
- 5) BX-2475, at a dosage of 50 mg/kg, severely restricted animals' growth, producing emaciation in females. BX-2487 at dose level of 50 mg/kg also limited animals' growth, but to a lesser degree.
- 6) Food consumption measurement in this study revealed adverse effects only in those rats receiving 50 mg/kg of either BX-2475 or BX-2487.
- 7) Compound BX-2326 appeared to have minimal toxicity with no apparent effect on either behavior or body weight gain. Food intake in males was slightly reduced.
- 8) No pathological abnormalities were observed during macroscopic postmortem examinations.
- 9) All three test articles (BX-2475, BX-2487 and BX-2326) when injected intraperitoneally at dose levels ranging from 2.5 to 50 mg/kg/day induced significant and clear cut peripheral nerve damage which was comparable with the Acrylamide control which was administered at a dose level of 10 mg/kg/day. The damaging effect of these compounds on the medulla oblongata did not appear to be significant.

REPORT OF FINDINGS ON SECTIONS OF EPON EMBEDDED,
TOLUIDINE BLUE STAINED NERVOUS TISSUE

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From all groups, 5 slides with at least two sections each were examined for tibial nerve, sciatic nerve and medulla oblongata respectively, and included cross and longitudinal sections. Examinations placed particular emphasis on such degenerative changes as fiber loss, endoneurial edema, folded corrugated myelin, myelin disintegration with intussusception, demyelination, abaxonal schwann cell cytoplasm, parano-dal myelin disintegration, tomaculum and ovoid formation, granular axoplasm and giant axonal swelling.

Overall, all peripheral tissues examined, in all groups, showed to a varying extent some or all of the changes as delineated above and which are usually associated with acrylamide intoxication. Specifically, very often only branches or parts of nerve branches were severely affected, with many of the remaining fibers unaffected.

It is important to note, that in some instances, despite considerable damage to peripheral nerve, fibers in the medulla oblongata, routinely showed no or only minor changes. Moreover, in some, cases, where such changes were present in medulla, it was not entirely clear whether they represented fixation artefact or were the result of control/test article intoxication. Specimens so affected are indicated in the detailed discussion below.

GROUP I (Acrylamide Control, 10 mg/kg)

Males:

Of the two animals examined, both tibial and sciatic nerves showed patchy but clear and pronounced change such as ovoids and giant axonal swellings, along with evidence of myelin dis-integration and associated corrugation as well as tomaculum formation. In some cases the degeneration was severe; and affected extensive areas of particular nerve branches. Fibers in the medulla were significantly involved in one case, whereas in the other animal, involvement was minimal.

Females:

Peripheral nerves were affected to about the same significant extent as the males, however, tissue from the medulla was unremarkable.

ME 0027

- 17 -

GROUP II (BX 2475, 2.5 mg/kg)

Males:

This group of 3 animals shows significant differences between animals. While 2 animals showed peripheral nerve damage which would be in keeping with the low dose of this group, the third male (#203) was extremely severely affected and showed typical signs of peripheral nerve damage, including extensive giant axonal swelling, ovoid and tomaculum formations. The fibers and cells in the medulla were unremarkable, despite the severe peripheral damage in #203.

Females:

As for males, again, with severe damage in one animal (#252), both in tibial nerve and in sciatic nerve. Medulla is unremarkable.

ME 0028

GROUP III (BX 2475, 10 mg/kg)

Males:

Despite the higher dose of compound #BX2475, compared to Group II, there was generally somewhat less damage compared to specimens examined in group II. These findings are also in keeping with the results of clinical examinations, with the possible exception of the female noted below. In all animals in this group, there was damage to myelin of single fibers scattered throughout the nerves, with severe damage in animals #301 and 351. In these latter two, damage was severe enough to include tomaculum formations.

Females:

As for males above, with #351 showing one severely affected branch in a sciatic nerve preparation.

-22-

GROUP IV (BX 2475, 50 mg/kg)

Males:

There is extensive involvement of fibers in all 3 males, with very severe damage in one branch of sciatic nerve in animal #402. While damage is extensive, characteristic giant axonal swelling is not pronounced, and damage is mainly evident as myelin folding, ovoid and tomaculum formation and demyelination. Medulla is minimally affected in #403, remainders unremarkable.

Females:

As for males, including comments on medulla.

GROUP V (BX 2487, 2.5 mg/kg)

Males:

Despite the low dose, there is extensive damage, especially evident in sciatic nerve of animal #501, with typical and extensive giant axonal swelling, ovoids, tomaculum formation and degeneration and corrugation of myelin. In these animals, some fibers in the medulla display evidence of myelin disintegration and possible ovoid formation.

Females:

Very similar to males with #551 severely affected. Again, there exists considerable inter-animal difference, with one animals (#551) severely affected, and another (#553) while positive for myelin and fiber damage, much less severely affected. Medulla in general is unremarkable.

GROUP VI (BX 2487, 50 mg/kg)

Males:

All three show pronounced peripheral nerve damage, with extensive involvement, including giant axonal swelling and extensive ovoid formation in #602 and #603. In the latter, in one instance 4 of 4 branches of the sciatic nerve are severely affected. Involvement of medulla is extremely minimal, with some moderate fiber damage in animal #603.

Females:

As for males above, with major sciatic nerve damage in #653 and some minimal myelin damage in medulla of #652 and #653.

GROUP VII (BX 2326, 50 mg/kg)

Males:

There is moderate to extensive involvement of several branches of both, sciatic and tibial nerves. Again, as in many other animals in this study, some sections revealed minor changes only, while other areas of the same nerve, in a different section, were profoundly damaged with characteristic lesions. Fibers in medulla are unremarkable.

Females:

As for males, above.

Conclusions

It is very evident that all three compounds under investigation (BX-2475; BX-2487 and BX-2326), when injected intraperitoneally, induced significant and clear cut peripheral nerve damage, consisting of the characteristic lesions described above. While the extent of the lesions appear to be dose related, it must be borne in mind that quantification of such damage, based upon examination of 10 (5×2) 1 μm thick sections per animal, does not permit an accurate prediction of the degree of involvement. Nevertheless, and with this reservation, the available data shows peripheral nerve damage in the following order, with damage decreasing from left to right.

7 > 1 > 5 > 6 > 4 > 2 > 3

It may be noted that this order is also borne out by the clinical findings (except in group VII) lending support to the dose dependent order of toxic effects of the administered compounds. While group VII appears to be sustained the most fiber damage, giant axonal swelling was not as pronounced as in other groups, and damage in general more diffuse.

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Assistant Professor

C. DeBonni
AUG 12th, 1980

NOTATION SYSTEM

BIO'S NOTATION

14	
13	-2.1
	-2.2
8	
7	-2.7
	-1.1
1	
4	-1.7
	0.1
7	
8	0.7
	1.1
42	
43	5.7
	6.1
70	
91	12.6
	12.7

weeks of treatment)

TABLE NO. 2

INCIDENCE OF CLINICAL SIGNS

MALES

GROUP NO.	LACRIMATION	SALIVATION	PILOECTION	WEAKENING		BODY TREMOR	STRENGTH
				TIP-TOE WALKING	HUNCH BACK		
I ACRYLAMIDE CONTROL 10 MG/KG	0	0	0	0	0	0	0
II BX-2475 2.5 MG/KG	0	0	1/5	0	0	0	0
III BX-2475 10 MG/KG	0	0	0	0	0	0	0
IV BX-2475 50 MG/KG	5/5	5/5	5/5	5/5	0	0	5/5
V BX-2487 2.5 MG/KG	1/5	0	0	0	0	0	0
VI BX-2487 50 MG/KG	4/5	5/5	0	0	0	2/5	0
VII BX-2326 50 MG/KG	1/5	0	0	0	0	0	0

The fractions reported above represent the number of rats on which signs of intoxication were observed on at least one occasion out of the total animals in each group during study periods.

TABLE NO. 3INCIDENCE OF CLINICAL SIGNSFEMALES

GROUP NO.	LACRIMATION	SALIVATION	PILOERCTION	TIP-TOE WALKING			BODY TREMOR	STRENGTH
				HIND LEG	BACK	WEAKENING		
I ACRYLAMIDE CONTROL 10 MG/KG	1/5	0	0	0	0	0	0	0
II BX-2475 2.5 MG/KG	0	0	0	0	0	0	0	0
III BX-2475 10 MG/KG	0	0	0	0	0	0	0	0
IV BX-2475 50 MG/KG	5/5	5/5	5/5	5/5	5/5	3/5	4/5	
V BX-2487 2.5 MG/KG	2/5	0	0	0	0	2/5	0	
VI BX-2487 50 MG/KG	4/5	3/5	1/5	1/5	1/5	0	0	
VII BX-2326 50 MG/KG	2/5	0	0	0	0	0	0	

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The fractions reported above represent the number of rats on which signs of intoxication were observed on at least one occasion out of the total animals in each group during study periods.

TABLE NO. 1

GROUP MEAN (S.D.) BODY WEIGHTS (G)

MALES

GROUP NO.	STUDY DAY					
	-2.1	-1.1	0.1	0.3	0.5	1.1
MALES						
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	127.6 12.66	155.8 18.59	186.8 23.74	192.8 23.98	194.0 24.04	201.4 26.18
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	133.0 17.16	163.4 15.63	194.0 14.54	198.8 15.01	198.2 14.39	204.6 13.58
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	130.6 11.72	164.4 13.79	194.4 15.22	196.0 15.33	197.4 15.32	202.8 15.27
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	130.8 5.65	157.4 6.19	185.4 7.44	184.0 8.00	178.8 8.76	185.8 9.88

(CONTINUED)

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TABLE NO. 4
(CONT'D.)

GROUP MEAN (S.D.) BODY WEIGHTS (G)

MALES

GROUP NO.	STUDY DAY							
	-2.1	-1.1	0.1	0.3	0.5	1.1	1.3	1.5
MALES								
GROUP V COMPOUND BX-2467 2.5 MG/KG/DAY	131.0 8.00	156.2 14.38	186.2 17.34	190.4 17.10	192.6 16.36	200.0 17.19	206.2 19.02	209.2 16.57
GROUP VI COMPOUND BX-2467 50 MG/KG/DAY	132.6 8.44	163.8 4.32	161.6 2.70	195.6 5.73	194.4 8.62	200.2 7.79	201.6 13.01	202.0 7.11
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	120.8 11.65	152.4 12.60	164.0 14.58	166.8 12.28	163.8 10.90	167.6 12.70	162.6 16.06	165.4 15.47

(CONTINUED)

12
13

TABLE NO. 5
(CONT'D.)

GROUP NO.	MALES	STUDY DAY						
		2.1	2.3	2.5	3.1	4.1	5.1	6.1
ACRYLAMIDE (CONTROL)								
10 MG/KG/DAY	27.73	27.49	27.09	26.91	30.12	26.59	27.95	26.92
COMPOUND BX-2475								
2.5 MG/KG/DAY	14.48	15.05	15.38	15.17	19.72	23.09	27.65	29.69
COMPOUND BX-2475								
10 MG/KG/DAY	17.33	17.80	16.85	16.37	21.53	22.19	23.47	24.14
COMPOUND BX-2475								
5.0 MG/KG/DAY	12.05	12.19	13.66	14.13	15.50	16.57	16.34	16.34

(CONTINUED)

TABLE NO. 4
(CONT'D.)

GROUP MEAN (S.D.) BODY WEIGHTS (G)

MALES

GROUP NO.	STUDY DAY							
	2.1	2.3	2.5	3.1	4.1	5.1		
MALES								
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	216.8 18.42	220.4 17.99	221.8 15.74	225.0 14.63	240.0 13.60	247.4 15.11	257.0 17.03	264.4 14.86
GROUP VI COMPOUND BX-2487 10 MG/KG/DAY	208.6 10.45	210.2 13.99	211.6 14.22	202.2 10.33	216.6 13.52	221.8 13.14	231.0 19.58	230.2 11.52
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	202.8 13.33	206.8 12.15	204.8 17.11	211.0 14.54	223.6 14.22	228.8 15.34	239.4 21.42	246.0 22.67

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(CONTINUED)

TABLE NO. 4
(CONT'D.)
GROUP MEAN (S.D.) BODY WEIGHTS (G)

MALES

GROUP NO.	STUDY DAY			BODY WEIGHT GAINS (G)		
	8.1	9.1	10.1	11.1	12.1	13.1*
GROUP I ACKYLANTIDE (CONTROL) 10 MG/KG/DAY						
	253.6	257.0	269.6	273.0	264.0	262.0
	26.52	27.01	27.21	25.34	26.59	25.28
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY						
	265.6	271.4	279.4	263.4	290.4	271.2
	30.52	32.53	34.72	35.59	34.11	26.76
GROUP III COMPOUND BX-2475 10 MG/KG/DAY						
	261.8	269.2	278.6	285.4	291.8	272.2
	26.37	28.39	25.91	26.12	29.58	27.53
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY						
	195.0	197.6	203.8	207.4	213.4	192.4
	20.22	20.27	20.13	16.12	16.02	16.27

3 * Fasting body weight.
(3)

(CONTINUED)

TABLE NO. 4
(CONT'D.)

MALES

GROUP NO.	STUDY DAY			BODY WEIGHT GAINS (G)			
	8.1	9.1	10.1	11.1	12.1	13.1*	0.1 - 13.1
GROUP V		STUDY DAY		BODY WEIGHT GAINS (G)		BODY WEIGHT GAINS (G)	
COMPOUND BX-2487		269.0	272.4	281.0	286.4	292.6	272.8
2.5 MG/KG/DAY		15.44	14.40	14.11	16.13	17.14	15.25
GROUP VI		STUDY DAY		BODY WEIGHT GAINS (G)		BODY WEIGHT GAINS (G)	
COMPOUND BX-2487		239.2	245.2	250.4	253.6	261.2	238.0
5.0 MG/KG/DAY		15.25	17.01	16.15	22.37	20.87	19.33
GROUP VII		STUDY DAY		BODY WEIGHT GAINS (G)		BODY WEIGHT GAINS (G)	
COMPOUND BX-2326		250.0	256.6	262.6	262.0	267.4	251.8
5.0 MG/KG/DAY		23.59	25.11	24.40	23.54	22.36	19.07

* Fasting Body Weight.

TABLE NO. 5

GROUP MEAN (S.D.) BODY WEIGHTS (G)

FEMALES

GROUP NO.	-	2.1	-1.1	0.1	0.3	0.5	1.1	1.3	1.5	STUDY DAY	
										W	W
GROUP I											
ACRYLAMIDE (CONTROL)	101.8	118.6	134.0	135.0	134.6	136.4	139.8	138.4			
10 MG/KG/DAY	12.91	6.03	5.32	4.85	6.14	5.18	4.82	5.37			
GROUP II											
COMPOUND BX-2475	107.2	124.8	139.6	139.4	139.8	145.4	146.0	146.8			
2.5 MG/KG/DAY	18.59	10.76	6.31	6.27	4.92	4.72	5.46	6.50			
GROUP III											
COMPOUND BX-2475	116.0	131.0	145.0	145.6	144.8	148.6	147.6	146.6			
10 MG/KG/DAY	3.39	3.67	5.61	4.62	5.07	5.73	6.03	5.73			
GROUP IV											
COMPOUND BX-2475	100.8	117.0	131.0	126.6	120.0	126.2	124.6	121.6			
50 MG/KG/DAY	23.98	17.89	16.54	16.21	13.53	13.41	14.19	11.97			

(CONTINUED)

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TABLE NO. 5
(CONT'D.) GROUP MEAN (S.D.) BODY WEIGHTS (G)

FEMALES

GROUP NO.	STUDY DAY					
	-2.1	-1.1	0.1	0.3	0.5	1.1
FEMALES						
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	113.6 6.54	125.2 4.21	138.2 5.54	140.0 5.83	140.2 6.53	145.4 6.54
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	107.6 10.16	121.6 8.23	134.4 7.86	138.0 9.38	137.8 8.96	140.4 8.29
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	108.2 5.40	123.6 4.98	135.4 5.13	137.6 6.88	137.8 5.36	140.8 5.54

(CONTINUED)

TABLE NO. 5
(CONT'D.)

FEMALES

GROUP NO.	STUDY DAY							
	2.1	2.3	2.5	3.1	4.1	5.1		
FEMALES								
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	143.2 7.01	142.2 7.85	141.2 7.01	143.2 7.50	147.2 8.70	150.6 10.41	152.6 13.01	152.2 9.20
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	149.0 5.34	150.4 4.93	150.6 6.43	150.6 7.19	154.6 9.29	157.2 7.98	157.2 7.53	160.4 8.82
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	152.0 7.38	152.2 6.83	152.4 8.65	154.2 9.50	156.2 7.85	159.2 5.72	159.0 8.97	161.2 9.01
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	127.2 14.99	127.0 16.45	124.4 17.08	126.0 17.52	129.4 16.27	128.0 17.04	129.8 16.92	130.8 16.27

(CONTINUED)

TABLE NO. 5
(CONT'D.)

GROUP MEAN (S.D.) BODY WEIGHTS

FEMALES

GROUP NO.	STUDY DAY						
	2.1	2.3	2.5	3.1	4.1	5.1	
<hr/>							
GROUP V COMPOUND UX-2487 2.5 MG/KG/DAY	151.4 7.30	152.6 7.96	151.6 8.71	153.2 9.23	160.0 9.51	157.6 10.83	161.0 12.63
GROUP VI COMPOUND UX-2487 50 MG/KG/DAY	147.2 8.41	149.2 9.09	149.4 5.41	149.0 6.06	154.6 9.53	154.4 9.40	157.2 9.93
GROUP VII COMPOUND UX-2326 50 MG/KG/DAY	147.0 6.16	148.4 6.54	149.2 7.98	151.4 6.19	155.6 5.77	155.8 6.14	160.4 5.03
<hr/>							

(CONTINUED)

TABLE NO. 5
(CONT'D.)

FEMALES

GROUP NO.	8.1	9.1	10.1	11.1	12.1	13.1*	STUDY DAY		BODY, WEIGHT GAINS (G)
							0.1 - 13.1		
FEMALES									
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	150.6 10.88	150.0 11.20	157.2 10.62	159.6 12.70	160.6 12.30	146.4 9.18	12.40 7.16		
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	159.0 10.51	159.2 10.50	164.2 11.52	160.8 11.78	166.8 10.83	153.8 9.04	14.20 5.63		
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	158.0 8.75	161.2 9.65	163.2 8.67	167.0 9.97	167.8 11.19	153.8 7.05	8.80 4.6		
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	130.6 17.01	128.6 14.45	133.0 15.76	133.2 14.10	136.6 13.81	118.0 12.27	-13.0 9.25		

* Fasting Body Weight.

(CONTINUED)

4

TABLE NO. 5
(CONT'D.)

GROUP MEAN (S.D.) BODY WEIGHTS (G)

FEMALES

GROUP NO.	STUDY DAY					BODY WEIGHT GAINS (G)	
	8.1	9.1	10.1	11.1	12.1		
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	162.6 12.78	165.8 12.89	167.8 14.13	169.0 10.51	171.6 11.93	159.8 12.11	21.6 6.88
GROUP VI COMPOUND BX-2487 5.0 MG/KG/DAY	157.8 10.99	160.6 13.07	157.8 11.43	162.0 10.75	165.4 9.96	149.4 14.05	15.0 11.0
GROUP VII COMPOUND BX-2326 5.0 MG/KG/DAY	158.6 5.13	161.2 6.26	164.2 6.83	161.6 6.99	166.2 8.70	151.6 3.51	16.20 2.17

* Fasting Body Weight.

TABLE NO. 6 GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)		
	-2.1 TO -1.1	-1.1 TO 0.1	0.1 TO 1.1
	2.1 TO 3.1	1.1 TO 2.1	1.1 TO 3.1
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	13.8 1.61	15.7 2.12	15.5 1.52
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	14.1 1.31	16.6 1.44	16.3 1.39
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	15.8 1.49	17.1 1.16	16.7 .95
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	14.7 1.13	15.7 1.55	14.1 1.50

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(CONTINUED)

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TABLE NO. 6 GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)
 (CONT'D.)

MALES

GROUP NO.	COMPOUND BX-2487 2.5 MG/KG/DAY	STUDY INTERVAL (DAYS)			40
		-2.1 TO -1.1	-1.1 TO 0.1	0.1 TO 1.1	
GROUP V	14.5 2.09	15.9 2.07	15.7 2.11	15.5 1.96	15.5 1.74
GROUP VI	15.1 .83	16.7 .92	14.0 1.16	13.8 .70	13.3 2.08
GROUP VII	15.0 .91	16.6 .99	14.1 3.10	15.7 1.75	15.3 3.12

(CONTINUED)

44

TABLE NO. 6
(CONT'D.) GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

MALES

GROUP NO.	ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	STUDY INTERVAL (DAYS)			41
		3.1 TO 4.1	4.1 TO 5.1	5.1 TO 6.1	
GROUP I		15.1 2.25	15.5 2.23	14.5 1.69	14.6 1.25
GROUP II	COMPOUND BX-2475 2.5 MG/KG/DAY	15.7 1.48	15.5 2.35	14.0 1.62	15.2 2.12
GROUP III	COMPOUND BX-2475 10 MG/KG/DAY	16.3 1.65	15.7 1.66	16.1 2.03	15.5 1.75
GROUP IV	COMPOUND BX-2475 50 MG/KG/DAY	14.7 2.16	15.7 5.74	11.7 2.03	12.2 1.45

(CONTINUED)

SF

TABLE NO. 6
(CONT'D.)

GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)		
	4.1 TO 4.1	5.1 TO 5.1	6.1 TO 7.1
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	15.7 .82	15.9 .81	14.7 2.80
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	14.0 3.03	14.3 1.83	- * -
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	15.7 1.90	15.5 1.50	14.2 1.58

*Balance Failure

(CONTINUED)

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TABLE NO. 6
(CONT'D.) GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

		MALES		STUDY INTERVAL (DAYS)			
		8.1 TO 9.1	9.1 TO 10.1	10.1 TO 11.1	11.1 TO 12.1	12.1 TO 13.1	
GROUP NO.							
GROUP I	ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	15.2 1.48	15.6 1.69	16.1 1.68	17.1 1.96	14.5 1.24	
GROUP II	COMPOUND BX-2475 2.5 MG/KG/DAY	15.5 2.07	13.2 1.18	16.0 2.60	16.2 1.91	13.9 1.73	
GROUP III	COMPOUND BX-2475 10 MG/KG/DAY	15.8 1.93	15.6 1.74	17.4 2.04	17.3 2.00	14.9 1.42	
GROUP IV	COMPOUND BX-2475 50 MG/KG/DAY	12.5 1.40	12.6 1.40	13.6 .83	13.9 .88	12.3 .97	

(CONTINUED)

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TABLE NO. 6 GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)
(CONT'D.)

MALES

GROUP NO.	COMPOUND BX-2487 2.5 MG/KG/DAY	STUDY INTERVAL (DAYS)			44
		8.1 TO 9.1	9.1 TO 10.1	10.1 TO 11.1	
GROUP V	15.5 1.09	15.2 .73	16.3 .76	16.9 1.02	14.2 .49
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	13.1 2.13	12.4 2.12	14.4 3.52	14.8 1.02	12.4 1.06
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	14.6 1.93	13.9 1.86	- * - -	13.8 4.25	13.0 .92

*Technical Error

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TABLE NO. ? GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

FEMALES

GROUP NO.	STUDY INTERVAL (DAYS)			45
	-2.1 TO -1.1	-1.1 TO 0.1	0.1 TO 1.1	
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	11.9 .98	12.4 3.86	12.3 .61	12.1 1.23
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	11.9 .88	13.0 .89	12.7 .33	12.1 .47
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	12.3 .74	13.4 .86	12.5 .67	12.6 1.00
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	11.4 1.43	12.1 1.38	9.1 .55	10.0 1.04

(CONTINUED)

TABLE NO. 7
(CONT'D.) GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

FEMALES

GROUP NO.	COMPOUND BX-2487 2.5 MG/KG/DAY	STUDY INTERVAL (DAYS)		
		-2.1 TO -1.1	-1.1 TO 0.1	0.1 TO 1.1
GROUP V	12.2 .28	12.7 .72	12.7 .74	11.7 .99
GROUP VI	11.7 .64	12.5 .48	10.9 .83	11.8 .49
GROUP VII	12.5 .53	12.9 .70	12.1 .42	12.2 .47

(CONTINUED)

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TABLE NO. ? GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)
(CONT'D.)

FEMALES

GROUP NO.	STUDY INTERVAL (DAYS)		
	3.1 TO 4.1	4.1 TO 5.1	5.1 TO 6.1
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	12.1 1.42	11.3 1.61	10.3 1.35
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	11.6 1.47	10.7 1.25	9.7 1.11
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	12.4 1.44	11.3 .72	10.1 1.33
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	9.9 1.26	9.8 1.79	10.4 .79

(CONTINUED)

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TABLE NO. 7
(CONT'D.)

GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

FEMALES

PAGE 00000000

GROUP NO.	COMPOUND BX-2487 2.5 MG/KG/DAY	STUDY INTERVAL (DAYS)			48
		4.1 TO 4.1	5.1 TO 5.1	6.1 TO 7.1	
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	11.8 1.45	11.7 2.40	9.1 2.33	9.4 .97	9.7 1.44
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	11.6 1.31	14.4 5.57	- * -	9.2 1.15	9.7 1.15
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	11.8 .87	11.4 .70	10.0 .30	10.2 1.57	10.1 .45

*Balance Failure

(CONTINUED)

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TABLE NO. 7 GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)
(CONT'D.)

FEMALES

		STUDY INTERVAL (DAYS)			
		8.1 TO 9.1	9.1 TO 10.1	10.1 TO 11.1	11.1 TO 12.1
GROUP NO.					13.1
GROUP I	ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	10.0 1.14	10.5 1.20	11.5 1.12	11.0 1.34
GROUP II	COMPOUND BX-2475 2.5 MG/KG/DAY	9.9 1.30	7.8 1.44	10.7 1.50	10.7 1.78
GROUP III	COMPOUND BX-2475 10 MG/KG/DAY	10.2 1.12	10.1 .88	11.3 1.09	10.6 .81
GROUP IV	COMPOUND BX-2475 50 MG/KG/DAY	8.9 1.04	9.6 1.45	10.0 1.06	10.7 1.15

(CONTINUED)

TABLE NO. 7 GROUP MEAN (S.D.) ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)
(CONT'D.)

FEMALES

GROUP NO.	STUDY INTERVAL (DAYS)		
	8.1 TO 9.1	9.1 TO 10.1	10.1 TO 11.1
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	10.4 1.33	10.3 1.37	11.3 1.14
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	9.8 1.68	8.8 .74	11.0 1.33
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	10.7 .79	9.9 .60	- * - -

*Technical Error

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TABLE NO. 8 GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)		
	-2.1 TO -1.1	-1.1 TO 0.1	0.1 TO 1.1
			1.1 TO 2.1
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	97.2 4.03	90.9 1.52	79.9 2.57
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	95.8 6.02	93.1 4.27	81.9 5.21
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	106.9 2.48	95.6 4.38	84.6 4.88
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	101.9 7.23	91.6 6.69	76.9 5.31

(CONTINUED)

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TABLE NO. 6
(CONT'D.)

GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)					
	-2.1 TO -1.1	-1.1 TO 0.1	0.1 TO 1.1	1.1 TO 2.1	2.1 TO 3.1	
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	100.3 9.77	92.2 4.75	81.7 4.05	74.3 4.49	70.2 4.76	
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	102.2 4.33	93.9 5.47	71.8 4.21	68.1 3.51	64.0 12.36	
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	110.4 7.40	98.7 3.57	76.0 16.99	80.6 4.70	74.0 13.16	

(CONTINUED)

TABLE NO. 8
(CONT'D.)

GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)			
	3.1 TO 4.1	4.1 TO 5.1	5.1 TO 6.1	6.1 TO 7.1
	58.4 3.51			
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	67.7 3.33	66.3 4.25	60.2 5.00	59.0 2.79
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	68.6 5.42	64.5 6.89	56.0 3.18	58.7 3.09
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	71.4 3.84	66.2 3.71	65.9 10.35	60.8 3.30
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	76.8 7.68	81.9 32.17	60.4 5.92	62.7 2.38
				59.0 3.04

(CONTINUED)

LAC 111.6
(CONT'D.)

GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES		STUDY INTERVAL (DAYS)			
GROUP NO.		3.1 TO 4.1	4.1 TO 5.1	5.1 TO 6.1	6.1 TO 7.1
GROUP V	COMPOUND BX-2487 2.5 MG/KG/DAY	67.4 3.47	65.5 2.55	58.1 9.52	55.6 2.46
GROUP VI	COMPOUND BX-2487 50 MG/KG/DAY	66.8 12.72	65.1 6.37	- * -	57.4 2.23
GROUP VII	COMPOUND BX-2326 50 MG/KG/DAY	72.3 7.30	68.2 2.74	60.4 2.30	56.0 3.67
*Balance Failure				61.3 6.32	56.5 3.30

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TABLE NO. 6
(CONT'D.)

GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)			- 55 -
	8.1	9.1	10.1	
	TO 9.1	TO 10.1	TO 11.1	
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	59.6 3.11	59.2 2.91	59.4 2.69	61.3 4.09
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	57.5 1.21	48.2 3.64	56.7 3.25	56.5 1.87
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	59.6 2.46	57.1 3.22	61.5 2.97	59.8 3.01
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	63.6 3.64	62.8 3.24	66.4 4.10	66.2 2.11
				60.6 2.59

(CONTINUED)

D

TABLE NO. 6
(CONT'D.) GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	COMPOUND BX-2487 2.5 MG/KG/DAY	STUDY INTERVAL (DAYS)		
		8.1 TO 9.1	9.1 TO 10.1	10.1 TO 11.1
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	57.1 3.18	55.0 2.12	57.6 1.67	58.5 1.34
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	54.1 5.71	49.9 5.70	56.5 8.79	57.7 2.43
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	57.3 2.66	53.3 3.67	- * - -	49.7 1.72
				* Technical Error

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TABLE NO. 9 GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

FEMALES

	-2.1 TO -1.1	-1.1 TO 0.1	0.1 TO 1.1	1.1 TO 2.1	2.1 TO 3.1
<hr/>					
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	108.2 12.38	97.8 29.30	90.6 3.44	86.8 6.78	78.0 5.36
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	103.3 9.51	98.6 4.93	90.3 2.04	82.6 3.03	72.9 5.28
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	98.5 5.66	97.2 3.45	85.6 1.98	84.3 3.47	78.4 6.66
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	106.5 14.43	98.4 6.79	72.9 6.14	80.8 4.14	76.4 4.41

(CONTINUED)

TABLE NO. 9
(CONT'D.) GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

		FEMALES			
GROUP NO.	10 MG/KG/DAY	4.1 TO 5.1	4.1 TO 5.1	5.1 TO 6.1	6.1 TO 7.1
GROUP I					
ACRYLAMIDE (CONTROL)	83.5 6.96	75.3 7.33	68.1 5.55	68.4 5.05	65.0 4.48
GROUP II					
COMPOUND BX-2475 2.5 MG/KG/DAY	75.9 5.43	68.2 4.74	61.8 5.94	65.1 4.72	60.6 4.01
GROUP III					
COMPOUND BX-2475 10 MG/KG/DAY	79.3 9.07	70.9 3.54	63.4 6.18	65.6 2.01	60.9 6.17
GROUP IV					
COMPOUND BX-2475 50 MG/KG/DAY	77.5 4.65	76.3 8.90	65.0 11.50	69.2 5.95	69.4 2.53

(CONTINUED)

TABLE NO. 9
 GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)
 (CONT'D.)

FEMALES

GROUP NO.	STUDY INTERVAL (DAYS)		
	3.1 TO 4.1	4.1 TO 5.1	5.1 TO 6.1
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	75.2 5.03	73.9 14.36	57.0 11.51
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	76.3 4.87	92.6 32.62	- * - -
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	76.9 5.90	73.0 3.37	63.3 2.52

* Balance Failure

(CONTINUED)

TABLE NO. 9
 (CONT'D.) GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)

FEMALES

GROUP NO.	10 MG/KG/DAY	2.5 MG/KG/DAY	10 MG/KG/DAY	2.5 MG/KG/DAY	10 MG/KG/DAY	50 MG/KG/DAY
GROUP I ACRYLAMIDE (CONTROL)	66.6 3.97	67.9 4.09	72.4 2.78	68.8 5.00	63.0 5.14	
GROUP II COMPOUND BX-2475	62.1 4.03	48.1 5.45	65.7 4.39	65.1 6.40	58.4 1.91	
GROUP III COMPOUND BX-2475	64.0 4.84	62.3 2.25	68.1 3.78	63.5 2.89	59.3 1.24	
GROUP IV COMPOUND BX-2475	68.9 3.16	73.0 3.93	75.1 4.68	79.3 4.98	66.4 4.69	

(CONTINUED)

TABLE NC. 9 GROUP MEAN (S.D.) RELATIVE FOOD CONSUMPTION (G/KG/DAY)
 (CONT'D.)

FEMALES

GROUP NO.		STUDY INTERVAL (DAYS)			- 62 -
		8.1 TO 9.1	9.1 TO 10.1	10.1 TO 11.1	
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	63.0 3.93	61.5 3.48	67.0 3.93	67.2 3.50	63.5 6.97
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	61.3 6.96	55.2 5.07	68.9 5.64	64.8 6.85	57.8 8.54
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	67.2 4.02	60.6 2.18	- * -	72.7 19.43	56.6 5.39

*Technical Error

FIGURE NO. 1

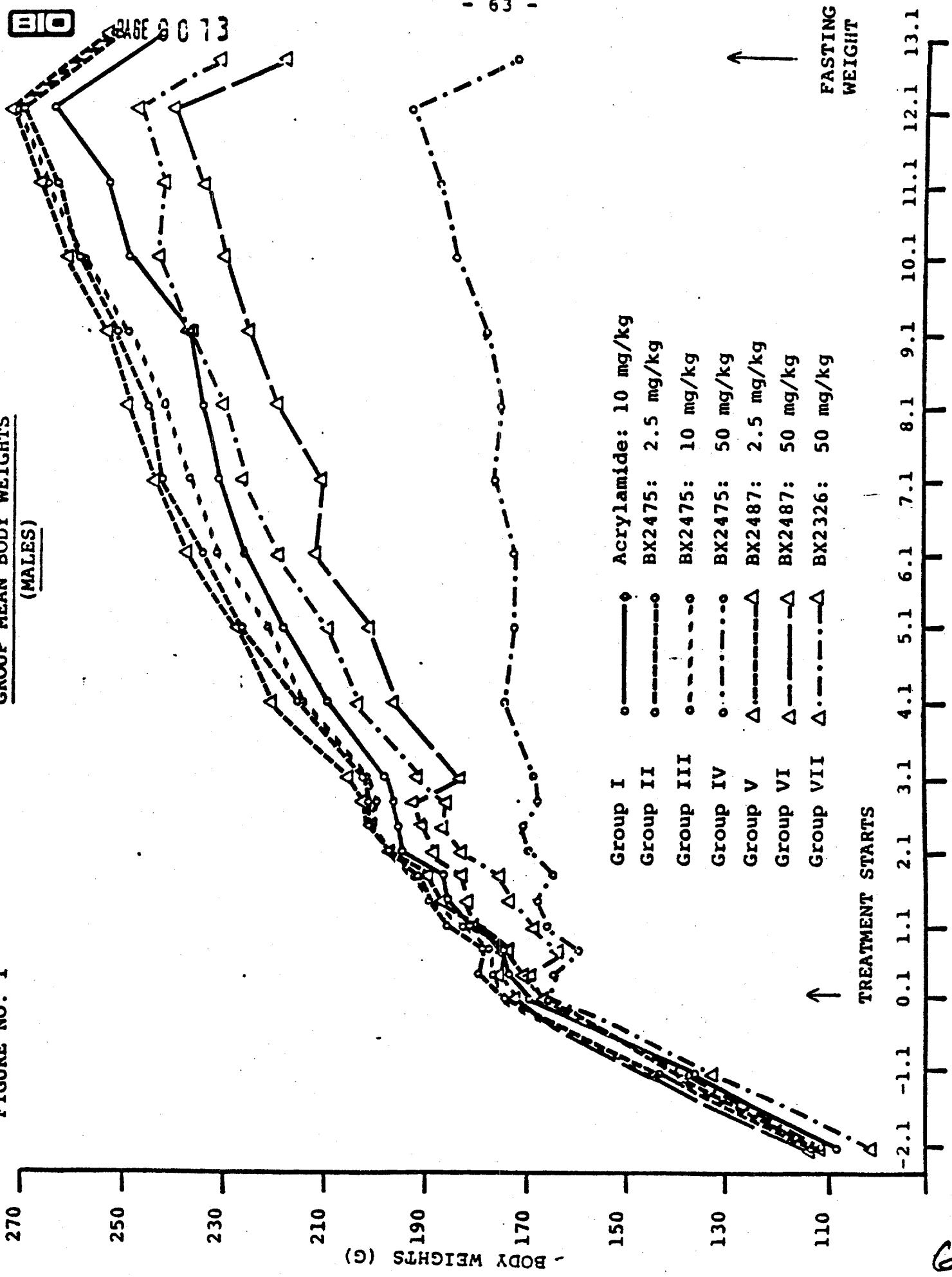
GROUP MEAN BODY WEIGHTS
(MALES)

FIGURE NO. II

GROUP MEAN BODY WEIGHTS
(FEMALES)

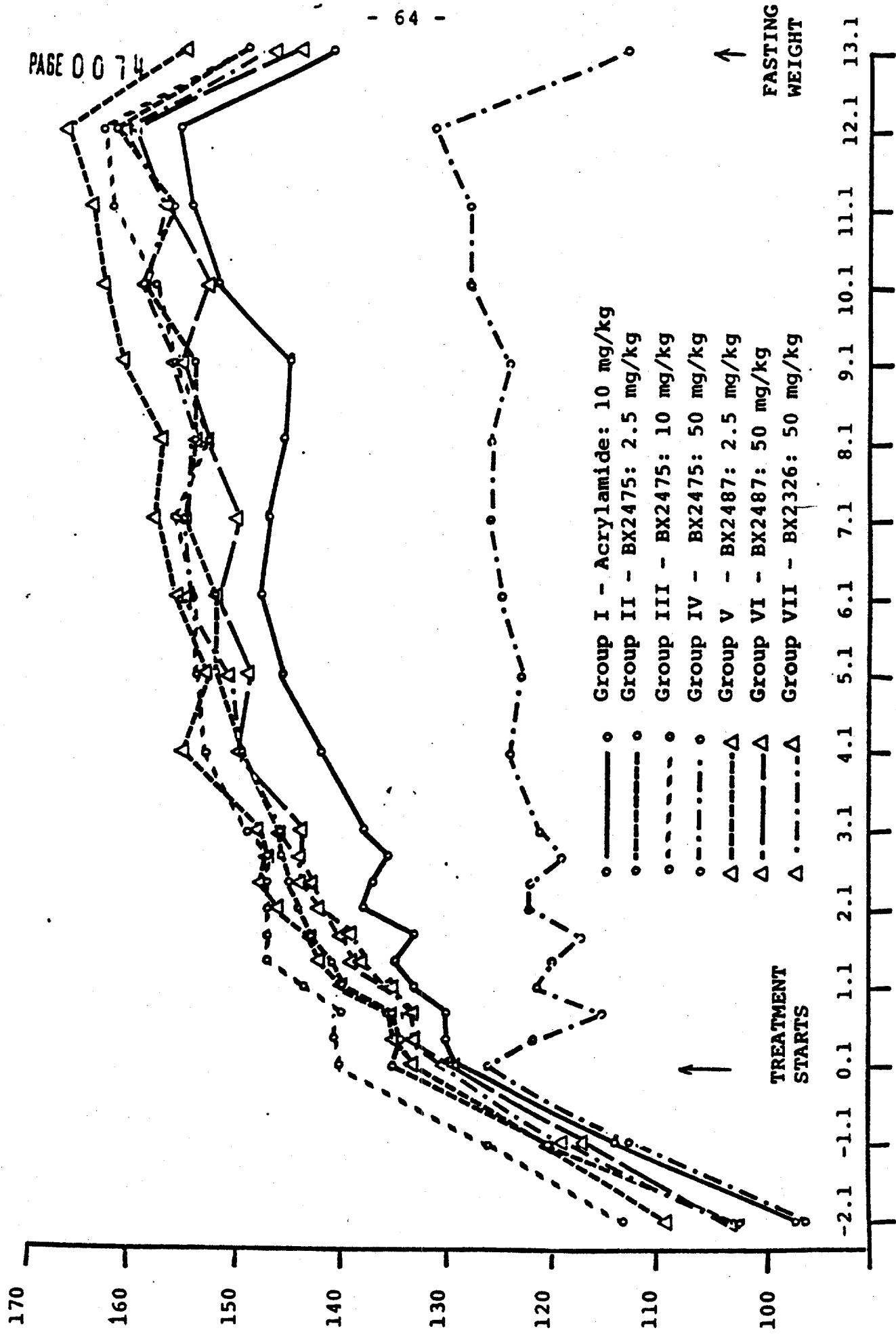
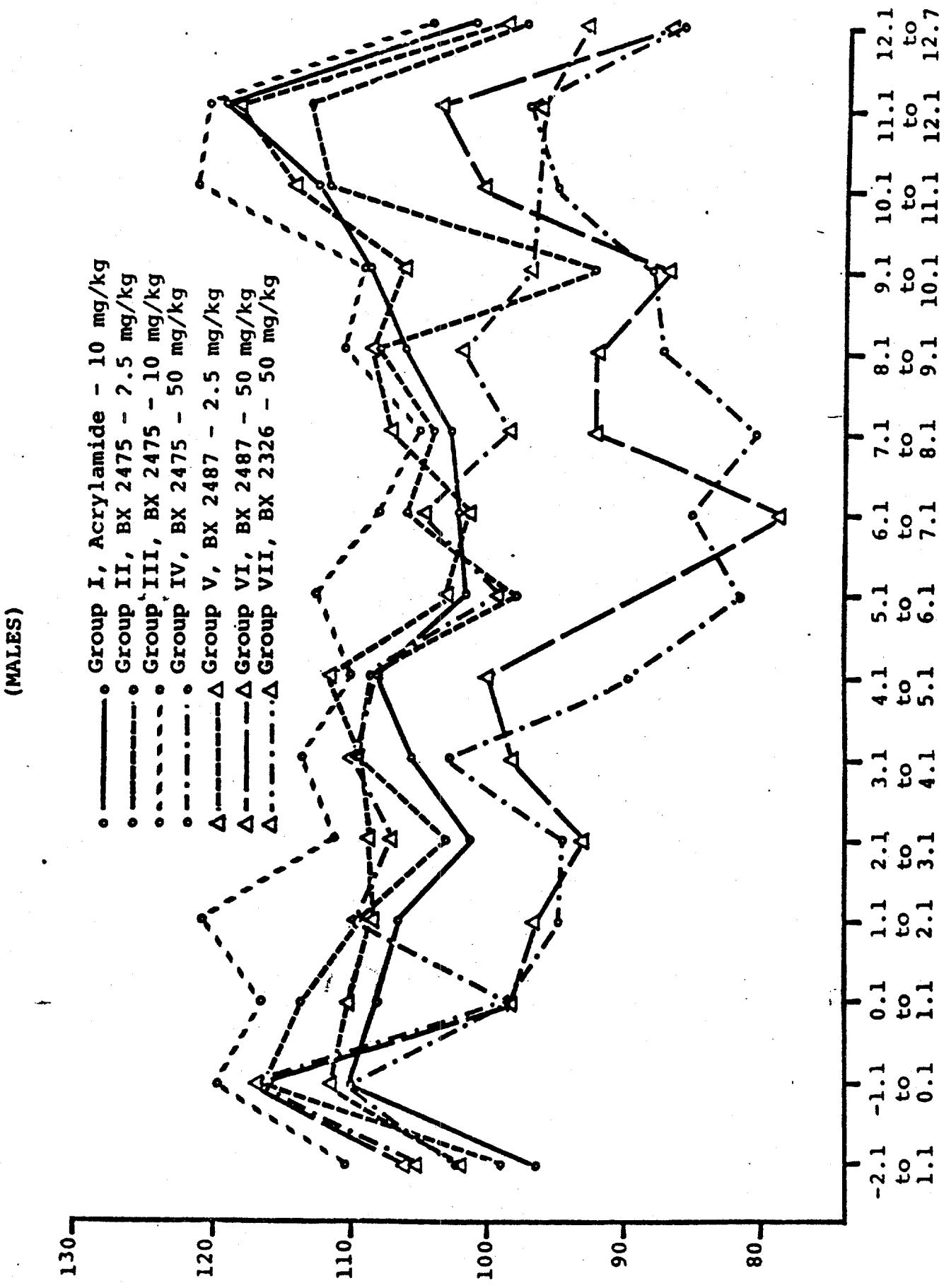


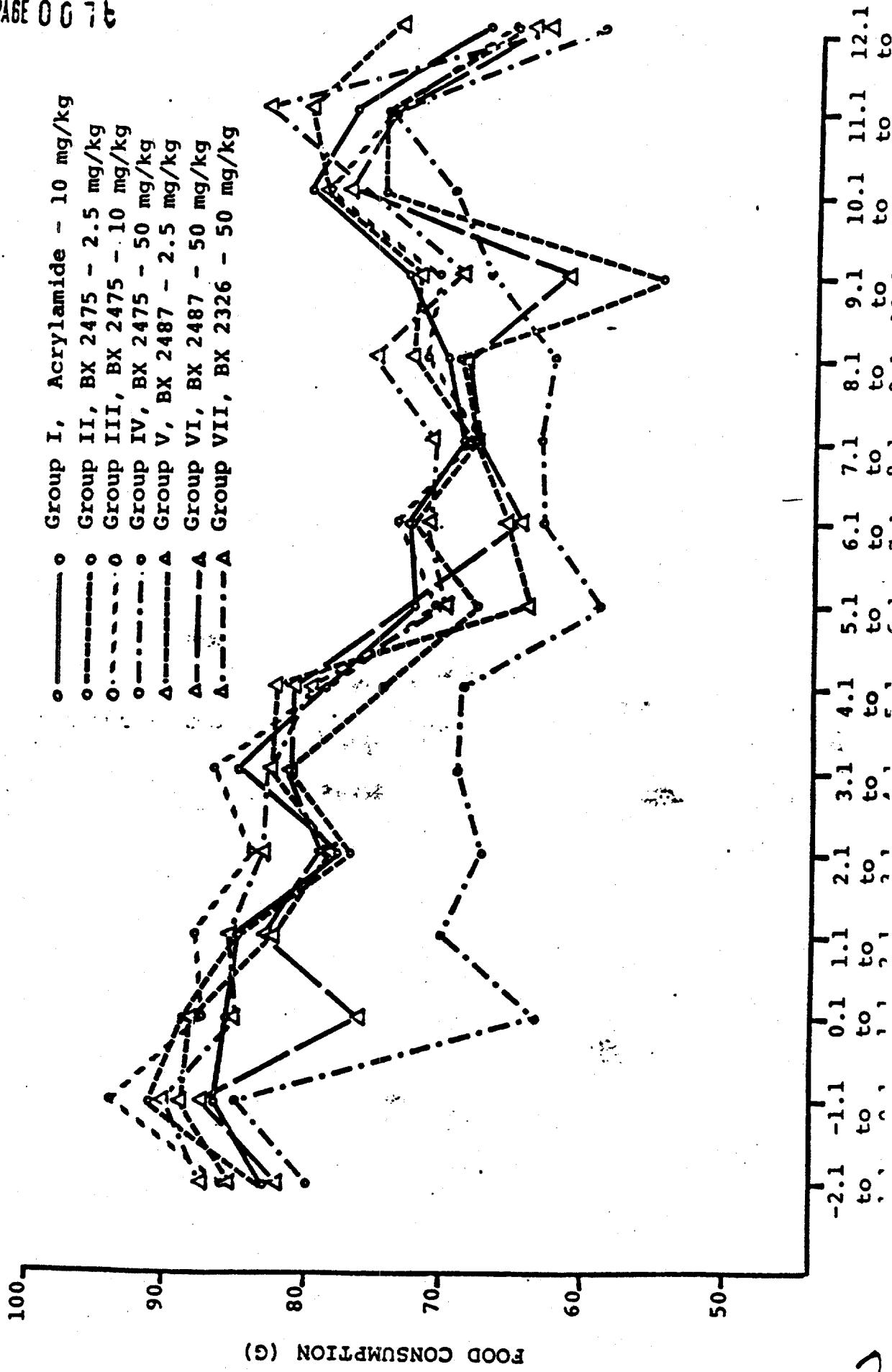
FIG. 11. **GROUP MEAN ABSOLUTE FOOD CONSUMPTION (G/RAT/WEEK)** **PROJECT 9088**



PAGE 007b

FIG. 7'
GROUP MEAN ABSOLUTE FOOD CONSUMPTION (G/RAT/WEEK)
(FEMALES)

PROJECT 9088



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APPENDIX I

ANALYSIS OF DIET
USED IN THIS STUDY

PAGE 110



(Continued - See Reverse Side)

CAUTION: Store in dry, well-ventilated areas free from insects and rodents. Do not use moldy or insect-infested feed. **IMPORTANT:** This product is a controlled nutrient rodent diet recommended for life cycle feeding of rats, mice and hamsters. An example of this product has been assayed for certain environmental contaminants. Maximum diet control is achieved by preanalysis monitoring of key nutrients and certain contaminating substances. Diet control helps minimize variability in research studies.

CERTIFICATION PROFILE: Based on analysis of a composite sample, each package contains not more than these maximum concentrations for the following substances:

Heavy Metals (Maximum Concentration)

- Arsenic 10 ppm
- Cadmium 15 ppm
- Lead 15 ppm
- Mercury 10 ppm
- Aluminum 10 ppm
- Chlorinated Hydrocarbons
- PCP 20 ppm
- Aldrin 10 ppm
- Dieldrin 10 ppm
- Ergotriol 10 ppm
- Heptachlor 10 ppm
- Heptachlor Epoxide 10 ppm
- Undecane 10 ppm
- Chlordane 10 ppm

DOT Related Substances

- CB 20 ppm
- CB 10 ppm

Organophosphates

- Thimet 10 ppm
- Disulfoton 10 ppm
- Methyl Parathion 10 ppm
- Malathion 10 ppm
- Parathion 10 ppm
- Thiodan 10 ppm
- Ethion 10 ppm
- Guthion 10 ppm

Drugs and Estrogens: This product is manufactured in a plant where antibiotics and synthetic estrogens are strictly prohibited. Routine monitoring for over a decade has not shown any detectable levels of these substances. No drugs or synthetic estrogens are permitted in manufacturing, storage, or warehousing to avoid any contamination of Lab-Chow diets.

Other Contaminants: If additional contamination assays are needed, these can be obtained by ordering such analyses prior to manufacture. Costs of these additional assays will be charged based on current analyses rates at time of assay.

BIO

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PAGE 001

APPENDIX I

CONTINUED



Checkerboard Square • St. Louis, Missouri 63188
KCPKU1

TO RICHMOND, IN

CC RICHMOND, IND.
F.C.SHELTON, 3KS
J.R.SNYDER, 2KS

LAB NO 522305 ENTERED 01/29/90 REPORTED 02/12/90 PHI

5002

CERTIFIED RECENT CHOW

LOT NUMBER JAN 24P02 G MEAL

ASSAY	ANALYSIS	UNITS	LOW-LIMIT	HIGH-LIMIT
PROTEIN (N X 6.25)	20.3	%	20.0	
DRIE				
FAT (ACID HYDRO.)	6.38	%	4.50	
STLM				
FIBER	4.47	%		5.50
FIBR				
ARSENIC	0.295	PPM		1.00
ASF				
CAUMIUM	0.125	PPM		0.50
CDF				
CALCIUM	0.942	%		
CAF				
LEAD	0.984	PPM		1.50
PB				
MERCURY				
PHOSPHORUS				
PF	0.796	%		
SELENIUM				
SE	0.325	PPM		
AFLATOXIN				
AFTC				
LESS THAN 10 PARTS PER BILLION TOTAL AFLATOXIN.				

ORGANIC PHOSPHATE TEST

ORG	(PPM)
THIMET	LESS THAN 0.02
DIZINCIN	LESS THAN 0.02
DISULFOTON	LESS THAN 0.02
METHYL PARATHION	LESS THAN 0.02
MALATHION	LESS THAN 0.02
PARATHICK	LESS THAN 0.02
THICLIN	LESS THAN 0.02
ETHION	LESS THAN 0.02

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APPENDIX I

CONTINUED

Raltech
SCIENTIFIC SERVICES
TM
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RT LAB NUMBER 533305

PAGE 2

CERTIFIED ROIDENT CHOW
LOT NUMBER JAN 24902 G MEAL

PESTICIDES & PCE

	RSPP (PPM)
HEPTACHLUR EPXIDE	LESS THAN 0.02
LLD-PIN	LESS THAN 0.02
HEPTACHLOR	LESS THAN 0.02
UIELURIN	LESS THAN 0.02
DDE	LESS THAN 0.02
DDT	LESS THAN 0.02
LINDANE	LESS THAN 0.02
CHLORLANE	0.02
END-PIN	LESS THAN 0.02
PCP	LESS THAN 0.15
ATP-EX	LESS THAN 0.02
METHOXYCHLOR	LESS THAN 0.02
ALPHA-BHC	LESS THAN 0.02
BETA-BHC	LESS THAN 0.02
DELTA-BHC	LESS THAN 0.02
HCF	LESS THAN 0.02

FOR ADDITIONAL INFORMATION, PLEASE CONTACT:

- (1) FOR ASSAY METHODOLOGY - CHARLIE SCHLECKER 314-992-2333
 - (2) FOR NUTRITIONAL INFORMATION - DR. D.C. SHELTON 314-992-3513
 - (3) ALL OTHER QUESTIONS - PICHMOND, IN., MANUFACTURING PLANT 317-962-9561
- THE LETTER CODE LOCATED BELOW EACH ASSAY IS A METHOD REFERENCE CODE

SIGNED C R Schlecker DATE 02/12/80

BY AND FOR RALTECH SCIENTIFIC SERVICES



January 23, 1980

ANALYSIS OF WATER
USED IN BIO-RESEARCH LAB

PAGE 0080

Subject: Analysis of distilled water and tap water

<u>Test</u>	<u>*Method</u>	<u>Limit of Detection</u>	<u>Distilled Water</u>	<u>Tap Water</u>
pH	424	0.00 - 14.00	6.65	6.50
Dissolved Solids	208A	5 ppm	< 5 ppm	22 ppm
Turbidity	214A	1 NTU	< 1 NTU	25. NTU
Alkalinity (as CaCO ₃)	403.4C	1 ppm (to pH 5.1)	10 ppm (to pH 5.1)	30 ppm (to pH 5.1)
Chlorides	108A	0.5 ppm	2 ppm	7 ppm
Ammonia Nitrogen	418B	0.04 ppm	< 0.04 ppm	< 0.04 ppm
Nitrates Nitrogen	419B	0.20 ppm	< 0.20 ppm	< 0.20 ppm
Nitrite Nitrogen	420.4	0.002 ppm	< 0.002 ppm	< 0.002 ppm
Total Phosphate	425.E	0.01 ppm	< 0.01 ppm	< 0.01 ppm
Total Sulfide	428	0.50 ppm	< 0.50 ppm	< 0.50 ppm
Phenols	510B	0.01 ppm	< 0.01 ppm	< 0.01 ppm
Organic Carbon	505	1.00 ppm	< 1.00 ppm	< 1.00 ppm
Arsenic	404A	0.01 ppm	< 0.01 ppm	< 0.01 ppm
Cadmium	305B	0.20 ppm	< 0.20 ppm	< 0.20 ppm
Total Iron	310A	0.20 ppm	< 0.20 ppm	3.0 ppm
Mercury	315B	0.10 ppm	< 0.10 ppm	< 0.10 ppm
Copper	308B	0.40 ppm	< 0.40 ppm	2.5 ppm
Lead	311B	0.50 ppm	< 0.50 ppm	< 0.5 ppm

* As per Standard Methods for the Examination of Water and Waste Water.

Pedro J. Araujo,
B.Sc.,
Head, Analytical Chemistry



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APPENDIX III

ANALYTICAL REPORT OF
CONTROL/TEST ARTICLE SOLUTIONS

RAPPORT ANALYTIQUE
ANALYTICAL REPORT

SOUMIS À:

SUBMITTED TO: Dr. B. Osborne
Dept. of Toxicology
Bio-Research Laboratories Ltd.

MATÉRIEL À ANALYSER:
TEST MATERIAL:

Control article mixture
acrylamide

PROJET NO:
PROJECT NO.: 9088

RAPPORT NO:
REPORT NO.:

DATE: January 25, 1980

DATE DE RÉCEPTION:
DATE RECEIVED: January 21, 1980

Description: Clear, colorless liquid.

*Assay (acrylamide): Label claim: 0.75%
Acrylamide found: 0.75%
% of claim: 100.0

* By HPLC

cc. S. Yong

/cf

Pedro J. Araujo, B.Sc.,
Head, Analytical Chemistry



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APPENDIX III CONT'D

RAPPORT ANALYTIQUE
ANALYTICAL REPORT

SOUMIS À:
SUBMITTED TO:

Dr. B. Osborne
Dept. of Toxicology
Bio-Research Laboratories Ltd.

MATÉRIEL À ANALYSER:
TEST MATERIAL: Control article mixture
acrylamide

PROJET NO.:
PROJECT NO.: 9088

RAPPORT NO.:
REPORT NO.:

DATE: April 17, 1980

DATE DE RÉCEPTION:
DATE RECEIVED: April 7, 1980

Description:

Clear, colorless liquid.

*Assay (acrylamide):

Label claim: 0.75%

Acrylamide found: 0.73%

% of claim: 97.3

* By HPLC

cc. S. Yong

Pedro J. Araujo, B.Sc.,
Head, Analytical Chemistry

/cf



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APPENDIX III CONT'D

RAPPORT ANALYTIQUE
ANALYTICAL REPORT

SOUMIS À:

SUBMITTED TO:

Dr. B. Osborne
Dept. of Toxicology
Bio-Research Laboratories Ltd.

MATÉRIEL À ANALYSER:

TEST MATERIAL:

Test article mixture
BX-2475

PROJET NO:
PROJECT NO.:

9088

RAPPORT NO.:
REPORT NO.:

DATE:

February 28, 1980

DATE DE RÉCEPTION:

DATE RECEIVED:

February 25, 1980

Description:

Clear, colorless liquid.

*Assay (BX-2475):

Label claim

BX-2475 found

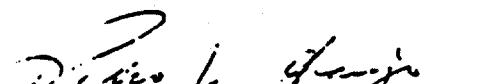
% of claim

0.1875%	0.189%	100.8
0.75%	0.748%	99.7
3.75%	3.74%	99.7

* By HPLC

cc. S. Yong

/cf


Pedro J. Araujo, B.Sc.,

Head, Analytical Chemistry



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APPENDIX III CONT'D

RAPPORT ANALYTIQUE ANALYTICAL REPORT

SOUmis à: Dr. B. Osborne **MATÉRIEL À ANALYSER:** Test article mixture
SUBMITTED TO: Dept. of Toxicology **TEST MATERIAL:** BX-2487
Bio-Research Laboratories Ltd.

PROJET NO: 9088
PROJECT NO.:

**RAPPORT NO.:
REPORT NO.:**

DATE: January 24, 1980

DATE DE RÉCEPTION: January 21, 1980
DATE RECEIVED:

Description: Clear, colorless liquid.

*Assay (BX-2487):	<u>Label Claim</u>	<u>BX-2487 found</u>	<u>% of claim</u>
	0.1875%	0.186%	99.2
	3.75%	3.73%	99.5

* By HPLC

cc. S. Yong

Pedro J. Araujo
Pedro J. Araujo, B.Sc.,
Head, Analytical Chemistry

/cf



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BIO-RESEARCH LABORATORIES LTD.

APPENDIX III CONT'D

RAPPORT ANALYTIQUE
ANALYTICAL REPORT

SOUMIS À:
SUBMITTED TO:

Dr. B. Osborne
Dept. of Toxicology
Bio-Research Laboratories Ltd.

MATÉRIEL À ANALYSER:
TEST MATERIAL:

Test article mixtu
BX-2487

PROJET NO.:
PROJECT NO.: 9088

RAPPORT NO.:
REPORT NO.:

DATE: April 17, 1980

DATE DE RÉCEPTION:
DATE RECEIVED: April 7, 1980

Description: Clear, colorless liquid.

*Assay (BX-2487):	Label Claim	BX-2487 found	% of claim
	0.1875%	0.180%	96.0
	3.75%	3.70%	98.7

* By HPLC

cc. S. Yong

/cf

Pedro J. Araujo, B.Sc.,
Head, Analytical Chemistry



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APPENDIX III CONT'D

RAPPORT ANALYTIQUE
ANALYTICAL REPORT

SOUMIS À:
SUBMITTED TO: Dr. B. Osborne
Dept. of Toxicology
Bio-Research Laboratories Ltd.

MATÉRIEL À ANALYSER:
TEST MATERIAL: Test article mixtur
BX-2326

PROJET NO.:
PROJECT NO.: 9088

RAPPORT NO.:
REPORT NO.:

DATE: February 28, 1980

DATE DE RÉCEPTION:
DATE RECEIVED: February 25, 1980

Description: Clear, colorless liquid.

*Assay (BX-2326):	<u>Label Claim</u>	<u>BX-2326 found</u>	<u>% of claim</u>
	3.75%	3.74%	99.7

* By HPLC

cc. S. Yong

Pedro J. Araujo, B.Sc.,
Head, Analytical Chemistry

/cf

ANALYSIS OF ACRYLAMIDE IN WATERAPPENDIX III CONT'DScope

This method was used to determine the concentration of acrylamide in water. The method uses normal high pressure liquid chromatography for separation and UV detection for quantitation.

Apparatus and Reagents

- A. acrylamide
- B. distilled water
- C. acetonitrile HPLC grade
- D. Waters High Pressure Liquid Chromatograph equipped with 6000A Pump, 254 nm U.V. detector, and Hewlett-Packard model 3380A electronic recording integrator.

Chromatographic Conditions

- A. Waters C₁₈, Radial compression A.
- B. Mobile phase: 90% distilled water/10% acetonitrile
- C. Flow Rate: 2.0 ml/ min
- D. Detector: 254 nm, 0.04 absorbance units full scale
- E. Attenuation: 16
- F. Injection volume: 50 microliters

ProcedureA. Preparation of mobile phase

1. Individually measure 900 ml of distilled water and 100 ml acetonitrile.
2. Mix in a suitable container, filter using a 0.5 micron teflon filter and de-gas for 15 minutes.

B. Preparation of Standard

1. Weigh into a 100 ml volumetric flask 0.75 g of acrylamide std., and add 75 ml distilled water.
2. Shake thoroughly.
3. Dilute to the 100 ml mark with distilled water.
4. Dilute 2.0 ml to 50 ml with distilled water.
5. Inject 50 mcl, recording the chromatogram and integrating each peak.

ANALYSIS OF METHYLENE-BIS-ACRYLAMIDE (BX-2475) IN WATERAPPENDIX III CONT'D

REF 0095

Scope

This method was used to determine the concentration of methylene-bis-acrylamide in water. The method uses normal high pressure liquid chromatography for separation of the components and UV detection for quantitation.

Apparatus and Reagents

- A. methylene-bis-acrylamide
- B. distilled water
- C. acetonitrile HPLC grade
- E. Waters High Pressure Liquid Chromatograph equipped with 6000A Pump, 254 nm U.V. detector, and Hewlett-Packard model 3380A electronic recording integrator.

Chromatographic Conditions

- A. Waters C₁₈, Radial compression A.
- B. Mobile phase: 90% distilled water/10% acetonitrile
- C. Flow Rate: 2.0 ml/ min
- D. Detector: 254 nm, 0.04 absorbance units full scale
- E. Attenuation: 16
- F. Injection volume: 50 microliters

ProcedureA. Preparation of mobile phase

1. Individually measure 900 ml of distilled water and 100 ml acetonitrile.
2. Mix in a suitable container, filter using a 0.5 micron teflon filter and de-gas for 15 minutes.

B. Preparation of Standard

1. Weigh into a 100 ml volumetric flask 3.75 g of compound (BX-2475) and add 75 ml distilled water.
2. Shake thoroughly.
3. Dilute to the 100 ml mark with distilled water.
4. Dilute 1.0 ml to 500 ml with distilled water.
5. Inject 50 mcl, recording the chromatogram and integrating each peak.

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ANALYSIS OF 2-HYDROXYETHYL ACRYLATE (BX-2487) IN WATER

APPENDIX III CONT'D

Scope

This method was used to determine the concentration of 2-hydroxyethyl acrylate in water. The method uses normal high pressure liquid chromatography for separation of the component and UV detection for quantitation.

Apparatus and Reagents

- A. 2-hydroxyethyl acrylate
- B. distilled water
- C. acetonitrile HPLC grade
- D. Waters High Pressure Liquid Chromatograph equipped with 6000A Pump, 254 nm U.V. detector, and Hewlett-Packard model 3380A electronic recording integrator.

Chromatographic Conditions

- A. Waters C₁₈, Radial compression A.
- B. Mobile phase: 90% distilled water/10% acetonitrile
- C. Flow Rate: 2.0 ml/min
- D. Detector: 254 nm, 0.04 absorbance units full scale
- E. Attenuation: 16
- F. Injection volume: 50 microliters

Procedure

A. Preparation of mobile phase

1. Individually measure 900 ml of distilled water and 100 ml acetonitrile.
2. Mix in a suitable container, filter using a 0.5 micron teflon filter and de-gas for 15 minutes.

B. Preparation of Standard

1. Weigh into a 100 ml volumetric flask 3.75 g of compound (BX-2487), and add 75 ml distilled water.
2. Shake thoroughly.
3. Dilute to the 100 ml mark with distilled water.
4. Dilute 5.0 ml to 100 ml with distilled water.
5. Inject 50 mcL, recording the chromatogram and integrating each peak.

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ANALYSIS OF 2-HYDROXYETHYL ACRYLATE
AND METHYLENE-BIS-ACRYLAMIDE (BX-2326) IN WATER

APPENDIX III CONT'D

Scope

This method was used to determine the concentration of 2-hydroxyethyl acrylate and methylene-bis-acrylamide in water. The method uses normal high pressure liquid chromatography for separation of the components and UV detection for quantitation.

Apparatus and Reagents ,

- A. 2-hydroxyethyl acrylate
- B. methylene-bis-acrylamide
- C. distilled water
- D. acetonitrile HPLC grade
- E. Waters High Pressure Liquid Chromatograph equipped with 6000A Pump, 254 nm U.V. detector, and Hewlett-Packard model 3380A electronic recording integrator.

Chromatographic Conditions

- A. Waters C₁₈, Radial compression A.
- B. Mobile phase: 90% distilled water/10% acetonitrile
- C. Flow Rate: 2.0 ml/min
- D. Detector: 254 nm, 0.04 absorbance units full scale
- E. Attenuation: 16
- F. Injection volume: 50 microliters

Procedure

A. Preparation of mobile phase

1. Individually measure 900 ml of distilled water and 100 ml acetonitrile.
2. Mix in a suitable container, filter using a 0.5 micron teflon filter and de-gas for 15 minutes.

B. Preparation of Standard

1. Weigh into a 100 ml volumetric flask 3.75 g of compound BX-2326 (mixture), and add 75 ml distilled water.
2. Shake thoroughly.
3. Dilute to the 100 ml mark with distilled water.
4. Dilute 2.0 ml to 25 ml with distilled water.
5. Inject 50 mcl, recording the chromatogram and integrating each peak.

C. Preparation of Sample

1. Dilute 2.0 ml to 25 ml with distilled water (for sample labelled 3.75%).
2. Shake thoroughly.
3. Inject 50 mcl, recording the chromatogram and integrating each peak.

APPENDIX III CONT'D

D. Calculations

$$* BX-2326 = \frac{\text{area spl}}{\text{area std}} \times \frac{\text{wt. std. (g)}}{1 \text{ ml}} \times \text{D.F.} \times 100 \text{ ml}$$

Where: area spl. = Total area of peaks of interest in sample

area std. = Total area of peaks of interest in standard

D.F. = Dilution factor ($\text{std}/100 \times 2/25 \times 25/2$) = $1/100$

Pedro J. Araujo
Pedro J. Araujo, B.Sc.,
Head, Analytical Chemistry

APPENDIX IV

INDIVIDUAL BODY WEIGHTS (G)

MALES

GROUP NO.	RAT NO.	STUDY DAY						
		-2.1	-1.1	0.1	0.3	0.5	1.1	1.3
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	101	127.0	156.0	196.0	199.0	204.0	214.0	221.0
	102	132.0	156.0	186.0	191.0	190.0	197.0	220.0
	103	128.0	151.0	164.0	189.0	190.0	195.0	195.0
	104	143.0	183.0	221.0	226.0	226.0	202.0	208.0
	105	108.0	131.0	155.0	159.0	160.0	236.0	236.0
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	201	105.0	139.0	170.0	173.0	174.0	182.0	188.0
	202	132.0	162.0	197.0	203.0	205.0	213.0	187.0
	203	135.0	162.0	193.0	200.0	196.0	216.0	221.0
	204	143.0	175.0	202.0	207.0	206.0	202.0	204.0
	205	150.0	179.0	208.0	211.0	208.0	211.0	219.0
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	301	143.0	179.0	213.0	215.0	214.0	221.0	223.0
	302	114.0	144.0	173.0	176.0	178.0	185.0	193.0
	303	133.0	164.0	189.0	189.0	196.0	193.0	194.0
	304	124.0	160.0	163.0	193.0	193.0	199.0	199.0
	305	139.0	175.0	204.0	207.0	212.0	216.0	205.0
GROUP IV COMPOUND BX-2475 5.0 MG/KG/DAY	401	138.0	162.0	189.0	185.0	180.0	188.0	227.0
	402	129.0	150.0	176.0	175.0	168.0	177.0	181.0
	403	129.0	153.0	179.0	177.0	172.0	175.0	175.0
	404	123.0	157.0	193.0	194.0	189.0	175.0	179.0
	405	135.0	165.0	190.0	169.0	185.0	190.0	191.0

(CONTINUED)

INDIVIDUAL BODY WEIGHTS (G)

MALES

STUDY DAY

GROUP NO.	RAT NO.	2.1	2.3	2.5	3.1	4.1	5.1	6.1	7.1
ACKYLAMIDE (CONTROL)									
10 MG/KG/DAY	101	233.0	235.0	231.0	239.0	254.0	264.0	269.0	271.0
	102	207.0	205.0	208.0	206.0	217.0	222.0	230.0	238.0
	103	215.0	216.0	218.0	221.0	233.0	247.0	254.0	256.0
	104	244.0	244.0	247.0	248.0	256.0	262.0	272.0	279.0
	105	172.0	174.0	175.0	175.0	183.0	197.0	206.0	212.0
COMPOUND BX-2475									
2.5 MG/KG/DAY	201	194.0	199.0	199.0	200.0	207.0	209.0	209.0	213.0
	202	226.0	236.0	236.0	234.0	257.0	267.0	277.0	280.0
	203	211.0	214.0	213.0	214.0	231.0	241.0	252.0	257.0
	204	222.0	223.0	223.0	224.0	231.0	249.0	258.0	272.0
	205	230.0	233.0	234.0	237.0	251.0	263.0	276.0	288.0
COMPOUND BX-2475									
10 MG/KG/DAY	301	237.0	241.0	239.0	244.0	250.0	254.0	260.0	263.0
	302	197.0	203.0	203.0	203.0	219.0	225.0	234.0	241.0
	303	206.0	204.0	202.0	202.0	212.0	219.0	225.0	230.0
	304	212.0	215.0	213.0	217.0	227.0	235.0	250.0	261.0
	305	233.0	236.0	240.0	236.0	263.0	273.0	285.0	293.0
COMPOUND BX-2475									
50 MG/KG/DAY	401	188.0	187.0	184.0	187.0	188.0	188.0	186.0	190.0
	402	163.0	161.0	175.0	178.0	184.0	182.0	177.0	183.0
	403	177.0	162.0	179.0	177.0	185.0	186.0	186.0	190.0
	404	209.0	211.0	210.0	212.0	221.0	222.0	224.0	236.0
	405	190.0	190.0	186.0	190.0	190.0	182.0	187.0	186.0

(CONTINUED)

APPENDIX IV
(CONT'D.)

INDIVIDUAL BODY WEIGHTS (G)

MALES

GROUP NO.	RAT NO.	STUDY DAY				
		8.1	9.1	10.1	11.1	12.1
MALES						
GROUP I ACETYLAINE (CONTROL) 10 MG/KG/DAY	101 275.0 102 237.0 103 262.0 104 278.0 105 216.0	278.0 238.0 263.0 285.0 221.0	290.0 247.0 276.0 299.0 236.0	290.0 255.0 278.0 302.0 240.0	299.0 264.0 289.0 317.0 251.0	277.0 242.0 263.0 295.0 233.0
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	201 215.0 202 264.0 203 261.0 204 276.0 205 292.0	218.0 291.0 266.0 281.0 301.0	222.0 297.0 275.0 291.0 312.0	226.0 302.0 275.0 296.0 318.0	235.0 304.0 286.0 301.0 326.0	224.0 284.0 268.0 280.0 300.0
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	301 208.0 302 243.0 303 230.0 304 270.0 305 258.0	279.0 245.0 237.0 278.0 307.0	288.0 261.0 246.0 285.0 313.0	293.0 265.0 251.0 295.0 323.0	299.0 271.0 255.0 303.0 331.0	281.0 253.0 238.0 280.0 309.0
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	401 190.0 402 179.0 403 192.0 404 230.0 405 184.0	165.0 183.0 190.0 233.0 187.0	201.0 185.0 195.0 239.0 195.0	206.0 195.0 199.0 239.0 198.0	210.0 196.0 209.0 244.0 208.0	192.0 176.0 188.0 220.0 184.0

(CONTINUED)

APPENDIX IV
(CONT'D.)

INDIVIDUAL BODY WEIGHTS (G)

MALES

GROUP NO.	RAT NO.	STUDY DAY	-2.1	-1.1	0.1	0.3	0.5	1.1	1.3	1.5
			-2.1	-1.1	0.1	0.3	0.5	1.1	1.3	1.5
GROUP V										
COMPOUND BX-2487	501	126.0	164.0	195.0	199.0	200.0	206.0	213.0	214.0	
2.5 MG/KG/DAY	502	128.0	149.0	172.0	175.0	178.0	182.0	186.0	187.0	
	503	144.0	176.0	205.0	210.0	213.0	222.0	231.0	234.0	
	504	133.0	163.0	195.0	198.0	199.0	207.0	213.0	216.0	
	505	124.0	139.0	164.0	170.0	174.0	183.0	188.0	195.0	
GROUP VI										
COMPOUND BX-2487	601	120.0	158.0	155.0	205.0	209.0	213.0	222.0	211.0	
50 MG/KG/DAY	602	134.0	162.0	190.0	193.0	193.0	202.0	206.0	206.0	
	603	129.0	163.0	188.0	192.0	194.0	194.0	198.0	201.0	
	604	139.0	169.0	193.0	191.0	188.0	195.0	188.0	192.0	
	605	141.0	167.0	192.0	197.0	166.0	197.0	195.0	200.0	
GROUP VII										
COMPOUND BX-2326	701	119.0	152.0	179.0	184.0	186.0	188.0	190.0	189.0	
50 MG/KG/DAY	702	136.0	167.0	200.0	191.0	183.0	173.0	172.0	177.0	
	703	117.0	151.0	186.0	194.0	174.0	192.0	200.0	206.0	
	704	124.0	159.0	193.0	204.0	201.0	206.0	215.0	216.0	
	705	106.0	133.0	162.0	171.0	175.0	179.0	166.0	189.0	

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(CONTINUED)

APPENDIX IV
(CONT'D.)

INDIVIDUAL BODY WEIGHTS (G)

BIO
EQUICO

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MALES

GROUP NO.	RAT NO.	STUDY DAY					
		8.1	9.1	10.1	11.1	12.1	13.1
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	501	275.0	277.0	288.0	295.0	304.0	284.0
	502	249.0	252.0	262.0	264.0	270.0	252.0
	503	291.0	292.0	300.0	307.0	314.0	291.0
	504	266.0	270.0	277.0	286.0	291.0	270.0
	505	264.0	271.0	278.0	280.0	284.0	267.0
GROUP VI COMPOUND BX-2487 5.0 MG/KG/DAY	601	264.0	273.0	282.0	292.0	298.0	271.0
	602	237.0	247.0	242.0	246.0	255.0	236.0
	603	236.0	237.0	245.0	241.0	248.0	224.0
	604	222.0	228.0	236.0	236.0	249.0	224.0
	605	237.0	241.0	247.0	253.0	256.0	235.0
GROUP VII COMPOUND BX-2326 5.0 MG/KG/DAY	701	213.0	218.0	225.0	222.0	232.0	226.0
	702	271.0	281.0	290.0	280.0	288.0	272.0
	703	270.0	277.0	277.0	278.0	285.0	269.0
	704	246.0	256.0	261.0	262.0	268.0	249.0
	705	250.0	252.0	260.0	260.0	264.0	243.0

APPENDIX V
(CONT'D.)

INDIVIDUAL BODY WEIGHTS (G)

FEMALES

STUDY DAY

GROUP NO.	RAT NO.	2.1	2.3	2.5	3.1	4.1	5.1	6.1	7.1
GROUP I ACRYLAMIDE (CONTROL)									
10 MG/KG/DAY									
151	145.0	146.0	144.0	141.0	149.0	153.0	154.0	155.0	
152	135.0	132.0	134.0	137.0	136.0	136.0	133.0	141.0	
153	153.0	153.0	152.0	156.0	160.0	165.0	168.0	165.0	
154	138.0	141.0	138.0	143.0	144.0	146.0	149.0	146.0	
155	145.0	139.0	138.0	139.0	147.0	151.0	159.0	154.0	
GROUP II COMPOUND BX-2475									
2.5 MG/KG/DAY									
252	142.0	144.0	142.0	142.0	144.0	146.0	155.0	154.0	
253	148.0	154.0	151.0	151.0	157.0	159.0	155.0	161.0	
254	157.0	156.0	160.0	162.0	169.0	169.0	170.0	175.0	
255	149.0	147.0	149.0	150.0	152.0	152.0	150.0	153.0	
GROUP III COMPOUND BX-2475									
10 MG/KG/DAY									
351	159.0	161.0	162.0	162.0	169.0	167.0	170.0	173.0	
352	144.0	143.0	140.0	140.0	147.0	151.0	145.0	148.0	
353	144.0	149.0	146.0	150.0	157.0	160.0	155.0	159.0	
354	157.0	156.0	158.0	163.0	158.0	160.0	160.0	163.0	
355	156.0	152.0	154.0	156.0	160.0	158.0	161.0	163.0	
GROUP IV COMPOUND BX-2475									
50 MG/KG/DAY									
451	128.0	131.0	127.0	131.0	132.0	135.0	133.0	135.0	
452	137.0	141.0	137.0	133.0	140.0	136.0	140.0	143.0	
453	122.0	120.0	119.0	121.0	125.0	125.0	124.0	124.0	
454	105.0	102.0	98.0	99.0	104.0	100.0	104.0	106.0	
455	144.0	141.0	141.0	146.0	146.0	144.0	148.0	146.0	

(CONTINUED)

APPENDIX V
(CONT'D.)

INDIVIDUAL BODY WEIGHTS (G)

FEMALES

GROUP NO.	RAT NO.	STUDY DAY				
		9.1	10.1	11.1	12.1	13.1
FEMALES						
GROUP I ACRYLONIDE (CONT'D.) 10 MG/KG/DAY	151 152 153 154 155	157.0 135.0 164.0 148.0 149.0	160.0 134.0 161.0 145.0 150.0	165.0 144.0 168.0 146.0 161.0	169.0 146.0 175.0 148.0 160.0	174.0 145.0 171.0 152.0 161.0
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	251 252 253 254 255	161.0 151.0 157.0 176.0 150.0	157.0 151.0 159.0 177.0 152.0	164.0 153.0 164.0 163.0 157.0	162.0 146.0 163.0 176.0 155.0	166.0 154.0 166.0 184.0 164.0
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	351 352 353 354 355	165.0 144.0 155.0 162.0 164.0	168.0 146.0 158.0 164.0 170.0	171.0 151.0 158.0 165.0 171.0	176.0 153.0 161.0 169.0 176.0	179.0 153.0 159.0 173.0 175.0
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	451 452 453 454 455	132.0 142.0 125.0 105.0 149.0	129.0 140.0 122.0 108.0 144.0	132.0 145.0 135.0 107.0 146.0	137.0 145.0 126.0 113.0 148.0	134.0 149.0 127.0 119.0 151.0

(CONTINUED)

APPENDIX VI
(CONT'D.)

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/KAT/DAY)

MALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		3.1	4.1	5.1	6.1	7.1	
		TO	TO	TO	TO	TO	b.1
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	101	16.7	17.0	15.3	16.3	15.6	
	102	13.1	13.0	12.3	13.7	13.1	
	103	16.1	16.7	14.9	14.7	16.1	
	104	17.3	17.6	16.7	15.3	15.4	
	105	12.3	13.1	13.6	13.1	13.3	
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	201	14.7	13.3	11.3	12.0	11.7	
	202	15.0	15.3	14.3	15.4	14.9	
	203	15.3	13.7	14.0	14.6	13.9	
	204	15.0	16.3	15.4	16.1	16.3	
	205	16.3	19.1	15.0	17.7	17.7	
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	301	16.6	15.3	14.6	14.9	14.0	
	302	15.9	15.4	14.1	15.1	14.0	
	303	14.1	13.9	16.6	13.1	13.3	
	304	16.0	15.7	15.3	16.3	15.9	
	305	18.7	18.4	18.0	17.9	18.0	
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	401	13.0	12.4	10.9	11.9	11.3	
	402	13.3	25.4	9.6	11.7	10.3	
	403	13.1	11.6	10.7	11.4	10.9	
	404	17.3	16.3	14.9	14.7	13.3	
	405	16.9	12.7	12.3	11.1	11.9	

(CONTINUED)

APPENDIX VI
(CONT'D.)

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

MALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		3.1	4.1	5.1	6.1	7.1	
		TO	TO	TO	TO	TO	
GROUP V							
COMPOUND BX-2487	501	15.7	15.4	15.0	15.0	16.0	
2.5 MG/KG/DAY	502	14.6	14.9	9.9	13.1	13.9	
	503	16.3	16.7	16.4	15.1	15.9	
	504	15.1	16.7	15.6	15.1	15.5	
	505	16.6	16.0	16.7	14.0	15.0	
GROUP VI							
COMPOUND BX-2487	601	17.6	16.9	*	11.7	15.3	
50 MG/KG/DAY	602	15.6	12.9	*	8.3	13.6	
	603	10.7	12.3	*	11.4	11.9	
	604	15.3	15.1	*	11.6	11.9	
	605	11.0	14.3	*	13.3	13.3	
GROUP VII							
COMPOUND BX-2326	701	13.4	13.4	11.7	11.4	11.1	
50 MG/KG/DAY	702	17.9	17.4	15.9	17.4	15.7	
	703	16.7	16.1	15.0	17.0	16.0	
	704	14.0	14.7	13.7	12.9	13.0	
	705	16.6	15.6	14.6	16.1	14.4	

* Balance Failure

(CONTINUED)

APPENDIX VI
(CONT'D.)

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

MALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		8.1 TO	9.1 TO	10.1 TO	11.1 TO	12.1 TO	
		9.1 TO	10.1 TO	11.1 TO	12.1 TO	13.1	
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY							
101	17.0	16.7	17.1	18.7	14.6		
102	13.4	13.3	13.9	14.4	13.1		
103	15.4	16.4	16.9	16.6	14.6		
104	16.1	17.1	17.9	18.1	16.4		
105	14.0	14.3	14.9	15.6	13.7		
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY							
201	12.1	11.9	12.3	13.1	11.1		
202	16.6	13.1	16.0	16.1	14.3		
203	14.9	12.3	15.1	16.3	13.9		
204	16.3	14.0	17.3	17.1	14.6		
205	17.4	14.7	19.3	18.3	15.9		
GROUP III COMPOUND BX-2475 10 MG/KG/DAY							
301	15.3	14.7	16.9	16.1	14.6		
302	14.3	15.1	16.9	16.1	14.4		
303	14.0	13.6	14.6	15.4	13.3		
304	17.0	16.7	18.6	18.3	15.3		
305	18.6	16.0	20.0	20.3	17.1		
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY							
401	13.3	13.0	14.0	14.1	13.0		
402	11.7	11.6	13.1	13.1	11.3		
403	11.3	11.1	12.4	13.9	11.6		
404	14.6	14.7	14.6	15.3	13.6		
405	11.6	12.6	13.9	13.1	12.0		

(CONTINUED)

APPENDIX VI
INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/KAT/DAY)
CONT'D.)

MALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)				
		8.1 TO	9.1 TO	10.1 TO	11.1 TO	12.1 TO
GROUP V						
COMPOUND BX-2487	501	16.7	15.9	17.1	17.6	14.6
.5 MG/KG/DAY	502	13.7	14.0	15.1	15.7	13.6
	503	15.4	15.3	16.7	18.0	14.7
	504	15.9	15.1	16.1	17.4	13.9
	505	15.6	15.7	16.6	16.0	14.4
GROUP VI						
COMPOUND BX-2487	601	16.9	15.9	20.4	16.4	14.0
0 MG/KG/DAY	602	12.0	10.1	13.4	13.7	12.9
	603	11.6	12.6	11.9	14.3	11.3
	604	12.7	11.6	12.0	14.7	11.9
	605	12.6	11.9	14.1	15.0	12.0
GROUP VII						
COMPOUND BX-2326	701	11.7	11.3	*	7.4	11.9
0 MG/KG/DAY	702	10.1	16.0	*	13.9	14.1
	703	16.4	14.4	*	16.0	13.4
	704	13.7	12.7	*	12.7	12.3
	705	14.9	14.9	*	18.9	13.3

Technical Error

APPENDIX VII

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		-2.1	-1.1	0.1	1.1	2.1	2.1
		TO	TO	TO	TO	TO	TO
ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	151 152 153 154 155	11.1 11.0 13.4 12.1 11.6	12.3 8.9 17.4 8.4 14.9	12.0 11.6 13.1 12.0 12.6	11.3 10.6 13.7 12.4 12.7	11.3 9.3 12.6 11.6 10.9	11.3 9.3 12.6 11.6 10.9
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	251 252 253 254 255	12.4 10.7 11.4 13.0 11.9	12.3 11.9 13.6 13.9 13.6	12.6 12.3 12.6 13.1 12.9	12.1 12.0 11.6 12.9 12.0	10.9 10.6 11.0 12.7 9.7	10.9 10.6 11.0 12.7 9.7
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	351 352 353 354 355	12.9 11.1 12.1 12.1 13.0	13.9 12.1 13.0 14.3 13.9	13.1 11.6 12.0 12.9 12.9	13.3 11.4 11.6 13.0 13.6	14.0 10.1 11.6 11.6 11.1	14.0 10.1 11.6 11.6 11.1
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	451 452 453 454 455	11.3 11.7 10.7 9.7 13.6	12.1 12.0 11.3 10.9 14.4	8.9 8.9 9.0 8.6 10.0	10.9 10.9 9.3 8.6 10.6	10.9 10.4 9.0 7.4 10.4	10.9 10.4 9.0 7.4 10.4

(CONTINUED)

APPENDIX VII
INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)
(CONT'D.)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		-2.1	-1.1	0.1	1.1	2.1	
		TO	TO	TO	TO	TO	TO
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY							
551	12.0	12.0	11.9	11.6	11.3		
552	12.0	12.3	12.4	10.9	8.9		
553	12.4	13.1	12.7	11.6	11.7		
554	12.0	12.3	12.4	11.3	10.6		
555	12.6	13.7	13.9	13.4	13.3		
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY							
651	12.0	12.3	11.0	11.6	12.7		
652	11.4	11.7	9.4	11.4	11.9		
653	12.6	12.9	11.1	12.3	10.3		
654	10.9	12.6	11.6	11.4	9.9		
655	11.6	12.9	11.1	12.4	11.4		
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY							
751	12.9	13.4	12.7	12.7	13.1		
752	11.9	11.9	11.9	11.9	11.3		
753	13.1	13.6	12.4	12.4	12.6		
754	12.1	12.6	11.7	11.6	11.7		
755	12.3	13.0	12.0	12.4	10.6		

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APPENDIX VII
(CONT'D.)

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		3.1 TO 4.1	4.1 TO 5.1	5.1 TO 6.1	6.1 TO 7.1	7.1 TO 8.1	- 111 -
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY							
151	11.3	11.4	10.4	11.4	10.9	10.9	
152	10.1	8.6	8.0	9.3	8.0	8.0	
153	13.7	12.7	11.1	11.1	10.6	10.6	
154	12.9	11.3	10.9	9.0	10.0	10.0	
155	12.7	12.3	11.3	11.3	11.3	9.9	
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY							
251	11.1	10.7	8.9	9.7	9.7	9.7	
252	10.3	9.4	10.4	9.9	8.9	8.9	
253	11.3	11.4	8.7	10.4	9.3	9.3	
254	14.1	12.3	11.3	12.6	11.9	11.9	
255	11.3	9.4	9.3	9.3	8.9	8.9	
GROUP III COMPOUND BX-2475 10 MG/KG/DAY							
351	12.9	11.4	11.0	11.3	10.1	10.1	
352	10.9	10.1	7.9	9.3	7.7	7.7	
353	14.4	12.0	10.4	10.4	10.4	9.3	
354	11.1	11.0	11.1	10.4	10.4	10.1	
355	12.6	11.7	10.1	11.1	11.1	11.4	
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY							
451	10.3	9.9	6.7	9.9	8.9	8.9	
452	11.0	12.6	10.7	10.7	10.3	10.3	
453	10.1	9.4	*	8.7	8.6	8.6	
454	7.7	7.6	7.0	6.9	7.6	7.6	
455	10.3	9.7	9.3	9.0	10.0	10.0	

* Balance Failure

(CONTINUED)

APPENDIX VII
(CONT'D.)

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		3.1	4.1	5.1	6.1	7.1	
		TO	TO	TO	TO	TO	TO
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	551	11.9	11.3	10.7	10.1	11.0	
	552	10.7	9.1	7.7	8.0	8.4	
	553	11.0	15.0	6.1	9.3	9.0	
	554	11.1	10.0	9.1	9.0	8.7	
	555	14.3	13.3	12.0	10.4	11.6	
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	651	13.4	11.6	*	10.6	10.1	
	652	11.1	17.0	*	10.0	10.1	
	653	12.4	23.0	*	7.6	11.0	
	654	10.1	9.9	*	8.9	8.0	
	655	10.9	10.6	*	9.1	9.1	
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	751	12.3	10.9	10.0	10.4	10.3	
	752	10.3	10.7	10.3	7.6	9.7	
	753	12.3	12.4	9.9	11.9	10.9	
	754	11.9	11.7	10.3	10.4	9.9	
	755	12.3	11.1	9.6	10.6	10.0	

* Balance Failure

(CONTINUED)

APPENDIX VII
(CONT'D.)

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)				
		8.1	9.1	10.1	11.1	12.1
		TO	TO	TO	TO	TO
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	151	11.4	11.7	12.9	12.3	10.0
	152	8.3	8.9	10.1	9.0	8.4
	153	10.4	10.9	12.1	11.4	9.3
	154	9.9	9.6	10.6	10.4	9.7
	155	10.1	11.3	11.7	12.0	10.9
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	251	9.4	8.0	10.4	10.1	9.1
	252	9.3	6.4	9.1	9.0	8.3
	253	9.9	7.7	10.9	10.1	9.4
	254	12.1	10.1	13.1	13.7	10.7
	255	8.9	6.9	10.0	10.6	9.3
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	351	10.3	10.7	11.9	11.4	10.3
	352	8.6	8.7	9.4	9.9	8.9
	353	10.1	10.0	11.4	10.3	8.9
	354	11.7	10.1	11.3	10.0	9.6
	355	10.4	11.0	12.3	11.6	10.1
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	451	9.4	9.6	9.4	10.1	7.7
	452	10.0	11.3	11.6	12.4	10.1
	453	8.3	8.9	9.6	9.7	8.4
	454	7.4	7.6	8.9	9.9	7.1
	455	9.4	10.6	10.4	11.3	8.9

(CONTINUED)

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)				
		8.1 TO 9.1	9.1 TO 10.1	10.1 TO 11.1	11.1 TO 12.1	12.1 TO 13.1
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY						
551	10.7	11.0	12.3	12.4		
552	9.4	8.9	10.7	10.6	10.4	
553	9.6	9.9	10.6	11.0	11.6	
554	9.6	9.4	10.1	10.3	9.4	
555	12.6	12.3	12.7	13.0	9.3	
GROUP VI COMPOUND BX-2487 5.0 MG/KG/DAY						
651	11.4	8.7	13.3	12.3	11.7	
652	10.3	9.6	10.4	11.6	9.4	
653	11.0	9.0	11.0	9.6	10.1	
654	7.3	7.6	9.9	10.0	7.9	
655	9.0	9.0	10.6	9.6		
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY						
751	11.1	10.1	*			
752	9.6	9.1	*	16.4		
753	11.4	10.4	*	12.1	8.1	
754	10.3	10.3	*	10.6	7.9	
755	11.3	9.3	*	12.3	9.4	
*Technical Error						
				8.0	9.6	
					10.0	
						- 114 -

APPENDIX VIII

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

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GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)			2.1 TO 3.1
		-2.1	-1.1	0.1	
		TO	TO	2.1	
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	101	93.9	92.5	81.1	74.2 71.5 76.0 76.2 71.7 77.2
	102	98.5	90.0	80.0	67.2 64.3 72.3 64.5 68.1
	103	92.2	89.6	79.2	
	104	99.9	92.6	76.2	
	105	101.6	89.9	83.2	
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	201	105.4	98.0	86.9	77.6 69.2 68.7 76.7 79.9
	202	90.4	87.5	76.9	63.5 64.3 66.6 71.0
	203	91.4	90.9	75.8	
	204	94.3	92.5	83.4	
	205	97.3	96.7	86.3	
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	301	108.3	89.7	77.0	76.4 82.3 81.1 83.2 88.1
	302	108.5	100.0	90.1	
	303	104.9	93.1	84.2	
	304	103.6	95.5	84.7	
	305	109.2	99.5	87.2	
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	401	98.1	89.5	79.0	71.2 73.6 70.1 79.6 70.8
	402	95.2	85.0	76.7	71.1
	403	98.3	89.5	70.1	66.9 81.4
	404	113.3	102.9	84.4	79.5 74.2
	405	104.8	90.9	74.5	

(CONTINUED)

APPENDIX VIII
(CONT'D.)

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)					
	-2.1		-1.1		0.1	
	TO	TO	TO	TO	TO	TO
501	113.3	96.3	82.9	72.9	69.2	69.2
502	101.1	89.9	78.4	68.7	66.8	66.8
503	101.8	91.5	88.2	74.4	68.4	68.4
504	99.4	97.4	80.3	81.2	78.6	78.6
505	85.8	85.8	78.7	74.4	68.2	68.2
601	100.7	93.9	75.6	65.1	44.4	44.4
602	98.5	89.3	75.1	65.8	62.1	62.1
603	109.6	102.6	71.3	70.2	75.4	75.4
604	102.0	94.7	65.1	66.2	73.6	73.6
605	100.2	89.1	71.7	73.3	64.9	64.9
701	116.0	101.9	88.3	79.8	71.1	71.1
702	97.4	92.6	48.2	73.4	91.1	91.1
703	113.0	99.2	72.3	85.2	80.6	80.6
704	112.1	99.0	81.5	79.9	71.8	71.8
705	113.6	100.7	89.6	84.5	55.5	55.5

(CONTINUED)

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		3.1	4.1	5.1	6.1	7.1	
		TO	TO	TO	TO	TO	
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	101	67.8	65.6	57.4	60.3	57.0	
	102	62.1	59.2	54.4	58.6	55.3	
	103	71.1	69.6	59.3	57.7	62.3	
	104	68.6	67.8	62.6	55.5	55.4	
	105	68.6	69.2	67.4	62.9	62.1	
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	201	72.3	63.9	54.0	56.9	54.7	
	202	61.1	58.3	52.5	55.4	52.7	
	203	68.7	58.1	56.8	57.3	53.5	
	204	65.9	67.9	60.9	60.9	59.4	
	205	74.9	74.5	55.7	62.8	61.1	
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	301	67.1	60.7	56.7	56.8	52.7	
	302	75.2	69.5	61.6	63.8	57.9	
	303	67.8	64.3	83.7	57.8	57.8	
	304	72.1	68.0	63.0	63.7	59.7	
	305	75.0	68.8	64.5	61.8	60.9	
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	401	69.3	66.1	58.1	63.1	59.4	
	402	73.4	139.0	53.3	65.1	56.8	
	403	72.6	62.4	57.6	60.8	56.8	
	404	79.8	73.5	66.6	64.8	57.8	
	405	88.7	68.4	66.6	59.7	64.1	

(CONTINUED)

APPENDIX VIII
(CONT'D.)

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		3.1	4.1	5.1	6.1	7.1	
		TO	TO	TO	TO	TO	
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	501	67.3	63.2	59.1	56.9	59.0	
	502	67.8	65.7	42.2	54.1	55.8	
	503	64.1	62.8	59.2	52.9	54.8	
	504	65.0	69.1	62.8	59.2	60.2	
	505	73.0	66.5	67.4	54.9	57.5	
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	601	79.3	70.4	*	45.9	59.8	
	602	72.1	57.3	*	36.3	58.9	
	603	51.4	59.4	*	50.5	50.8	
	604	76.0	70.9	*	54.2	54.1	
	605	55.0	67.5	*	57.9	56.5	
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	701	67.0	65.7	57.0	54.9	52.7	
	702	78.5	72.2	62.8	66.0	58.3	
	703	72.2	67.8	60.6	65.6	60.2	
	704	63.3	65.8	59.5	53.9	53.3	
	705	80.4	69.7	62.1	66.2	57.9	

*Balance Failure

(CONTINUED)

APPENDIX VIII
(CONT'D.)

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

MALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		8.1	9.1	10.1	11.1	12.1	
		TO	TO	TO	TO	TO	
10 MG/KG/DAY	9.1	10.1	11.1	12.1	13.1		
GROUP I ACRYLAMIDE (CONTROL)	101	61.5	58.9	59.1	63.5	50.6	
	102	56.5	54.8	55.2	55.6	51.9	
	103	58.8	61.0	60.9	65.5	52.8	
	104	57.3	58.7	59.4	58.6	53.7	
	105	64.1	62.5	62.4	63.4	56.7	
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	201	56.1	53.9	54.8	57.0	48.6	
	202	57.6	44.7	53.4	53.3	48.6	
	203	56.4	45.4	55.1	58.1	50.0	
	204	58.5	49.0	58.9	57.4	50.2	
	205	58.8	48.0	61.2	56.8	50.7	
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	301	55.9	51.9	58.0	54.5	50.2	
	302	58.5	59.9	64.1	60.2	55.1	
	303	60.0	56.2	58.6	61.0	53.9	
	304	62.0	59.4	64.0	61.2	52.4	
	305	61.4	58.1	62.9	62.0	53.6	
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	401	69.0	65.7	68.8	68.0	64.7	
	402	64.7	62.2	68.5	67.2	60.4	
	403	59.1	57.9	63.1	67.9	58.3	
	404	62.9	62.3	61.0	63.3	58.5	
	405	62.4	65.8	70.5	64.7	61.2	

(CONTINUED)

APPENDIX VIII
INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)
(CONT'D.)

MALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)				
		8.1	9.1	10.1	11.1	12.1
		TO	TO	TO	TO	TO
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	501	60.6	56.1	58.8	58.7	49.6
	502	54.7	54.5	57.6	58.9	52.0
	503	52.9	51.6	55.1	58.0	48.6
	504	59.2	55.4	57.3	60.4	49.4
	505	58.2	57.2	59.4	56.7	52.4
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	601	62.8	57.1	71.2	55.7	49.2
	602	49.6	41.5	55.0	54.7	52.4
	603	48.9	52.2	48.8	58.4	47.8
	604	56.5	49.9	50.8	60.7	50.1
	605	52.6	48.6	56.6	58.9	48.9
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	701	54.4	51.0	*	32.7	51.8
	702	58.5	56.0	*	48.8	50.5
	703	60.1	52.1	*	56.8	48.5
	704	54.6	49.2	*	48.0	47.5
	705	59.2	58.0	*	70.9	52.4

*Technical Error

APPENDIX IX

RELATIVE FOOD CONSUMPTION (G/KG/DAY)

FEMALES

INDIVIDUAL

STUDY INTERVAL (DAYS)

GROUP NO.	RAT NO.	-2.1			-1.1			0.1			1.1			2.1		
		TO			TO			TO			TO			TO		
		-1.1			0.1			1.1			2.1			3.1		
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	151	93.6			94.5			86.7			80.2			78.2		
	152	99.5			71.4			87.7			78.7			69.3		
	153	119.9			130.6			91.6			92.6			82.1		
	154	106.1			67.4			91.7			91.3			82.8		
	155	121.8			124.8			95.2			91.5			77.7		
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	251	101.0			90.0			88.0			82.4			72.2		
	252	119.0			100.9			93.4			87.0			74.1		
	253	95.2			102.4			90.2			79.5			72.6		
	254	104.4			100.1			90.7			84.1			80.2		
	255	96.8			99.8			89.1			80.2			65.4		
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	351	101.6			97.2			87.3			85.8			86.9		
	352	91.3			92.0			82.9			81.0			71.6		
	353	99.9			96.3			84.6			80.9			78.2		
	354	94.1			100.3			85.5			84.9			83.2		
	355	105.3			100.4			87.8			89.1			72.4		
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	451	94.8			92.7			68.1			85.4			84.1		
	452	101.0			94.1			69.0			83.4			75.8		
	453	99.2			96.0			75.3			77.5			74.9		
	454	131.3			109.7			82.7			82.2			73.8		
	455	106.4			99.5			69.5			75.5			73.3		

(CONTINUED)

APPENDIX IX
(CONT'D.)

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

FEMALES

GROUP NO.	STUDY INTERVAL (DAYS)					
	-2.1	-1.1	0.1	1.1	2.1	
	TO	TO	TO	TO	TO	
RAT NO.	-1.1	0.1	1.1	2.1	3.1	
551	98.0	90.6	85.4	78.9	74.7	
552	105.3	97.1	92.8	77.5	62.4	
553	105.8	100.7	91.3	79.1	78.2	
554	103.4	94.9	88.4	76.6	69.2	
555	99.0	98.3	92.1	84.7	80.5	
651	97.6	91.7	76.7	77.8	82.9	
652	108.3	99.3	75.2	86.6	84.6	
653	99.8	93.2	75.2	79.9	64.8	
654	99.6	100.2	84.0	79.7	67.1	
655	105.2	102.9	83.2	88.7	78.6	
751	110.4	103.3	91.5	87.1	87.9	
752	105.4	93.7	86.8	82.6	76.0	
753	105.6	98.3	84.6	81.2	78.8	
754	107.9	98.6	86.9	82.9	80.1	
755	108.2	103.6	91.0	89.6	75.0	

(CONTINUED)

APPENDIX IX
(CONT'D.)

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

FEMALES

STUDY INTERVAL (DAYS)

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)		
		3.0 TO 4.1	4.1 TO 5.1	5.1 TO 6.1
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	151	77.8	75.7	67.9
	152	74.3	63.0	59.5
	153	86.8	78.2	66.9
	154	89.6	77.3	73.1
	155	88.9	82.5	72.8
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	251	74.3	69.3	56.4
	252	71.9	64.6	68.8
	253	73.3	72.3	55.5
	254	85.5	72.7	66.6
	255	74.7	62.0	61.5
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	351	77.7	68.0	65.3
	352	75.7	68.1	53.1
	353	94.0	75.7	65.4
	354	69.4	69.2	69.6
	355	79.6	73.7	63.6
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	451	78.2	73.8	50.1
	452	80.6	91.1	77.6
	453	82.5	75.4	*
	454	76.0	74.2	68.6
	455	70.5	67.0	63.6

* Balance Failure

(CONTINUED)

APPENDIX IX
(CONT'D.)

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		3.1	4.1	5.1	6.1	7.1	
		TO	TO	TO	TO	TO	TO
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY	551	75.8	70.8	66.1	61.1	65.3	
	552	73.6	62.2	53.8	55.4	57.9	
	553	71.9	97.4	39.4	58.2	56.3	
	554	71.0	62.9	57.5	55.6	54.0	
	555	83.5	76.1	68.2	58.8	65.0	
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY	651	83.7	70.3	*	63.1	60.2	
	652	76.6	114.5	*	65.6	66.1	
	653	76.7	139.4	*	46.6	67.5	
	654	70.4	66.6	*	59.4	54.1	
	655	73.9	72.2	*	61.2	61.2	
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY	751	78.8	69.8	63.7	65.2	64.5	
	752	67.9	68.9	64.5	48.1	63.3	
	753	75.8	75.6	59.2	70.6	64.8	
	754	78.0	75.6	65.9	65.8	62.0	
	755	84.1	75.3	63.2	67.5	63.9	

* Balance Failure

(CONTINUED)

APPENDIX IX
(CONT'D.)

INDIVIDUAL
RELATIVE FOOD CONSUMPTION (G/KG/DAY)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)					
		8.1	9.1	10.1	11.1	12.1	
		TO	TO	TO	TO	TO	
GROUP I ACRYLAMIDE (CONTROL) 10 MG/KG/DAY	151	72.1	72.1	77.0	71.6	61.0	
	152	61.6	63.7	70.0	61.9	60.2	
	153	64.2	66.0	70.8	66.1	57.1	
	154	67.3	65.3	71.4	69.5	67.0	
	155	67.8	72.6	73.0	74.8	69.6	
GROUP II COMPOUND BX-2475 2.5 MG/KG/DAY	251	59.3	49.8	64.0	61.8	57.3	
	252	61.5	42.3	61.2	60.0	55.8	
	253	62.4	47.8	66.4	61.7	58.9	
	254	68.8	56.3	72.8	75.8	60.9	
	255	58.7	44.4	64.1	66.3	59.0	
GROUP III COMPOUND BX-2475 10 MG/KG/DAY	351	61.8	63.2	68.3	64.4	60.2	
	352	59.1	58.7	62.0	64.4	59.2	
	353	64.8	63.3	71.7	64.3	57.1	
	354	71.9	61.7	67.6	58.5	58.9	
	355	62.4	64.5	70.8	65.9	60.7	
GROUP IV COMPOUND BX-2475 50 MG/KG/DAY	451	72.2	73.3	71.4	75.4	61.5	
	452	70.9	79.2	79.8	84.5	72.7	
	453	67.1	68.9	72.8	76.2	69.7	
	454	69.8	70.4	80.5	85.0	64.9	
	455	64.4	72.9	70.9	75.5	63.0	

| (CONTINUED)

APPENDIX IX
(CONT'D.)

INDIVIDUAL

RELATIVE FOOD CONSUMPTION (G/KG/DAY)

FEMALES

GROUP NO.	RAT NO.	STUDY INTERVAL (DAYS)				
		8.1 TO	9.1 TO	10.1 TO	11.1 TO	12.1 TO
		9.1 10.1	10.1 11.1	11.1 12.1	12.1 13.1	13.1
GROUP V	551	63.0	64.5	71.4	71.6	61.9
COMPOUND BX-2487	552	63.9	59.0	69.6	66.5	75.1
2.5 MG/KG/DAY	553	59.6	60.5	64.5	66.7	59.3
	554	59.4	57.7	61.7	62.1	57.3
	555	69.1	65.7	67.8	69.0	64.1
GROUP VI	651	66.6	51.3	77.9	70.0	68.9
COMPOUND BX-2487	652	65.7	60.8	66.4	72.3	61.2
50 MG/KG/DAY	653	64.0	51.9	63.8	55.0	59.8
	654	49.6	51.5	65.7	64.7	52.6
	655	60.4	60.8	70.7	62.0	46.6
GROUP VII	751	69.2	61.7	*	101.1	51.5
COMPOUND BX-2326	752	62.0	58.2	*	78.3	51.7
50 MG/KG/DAY	753	67.6	60.3	*	60.2	56.3
	754	64.7	63.7	*	73.8	59.3
	755	72.3	59.0	*	50.0	64.3

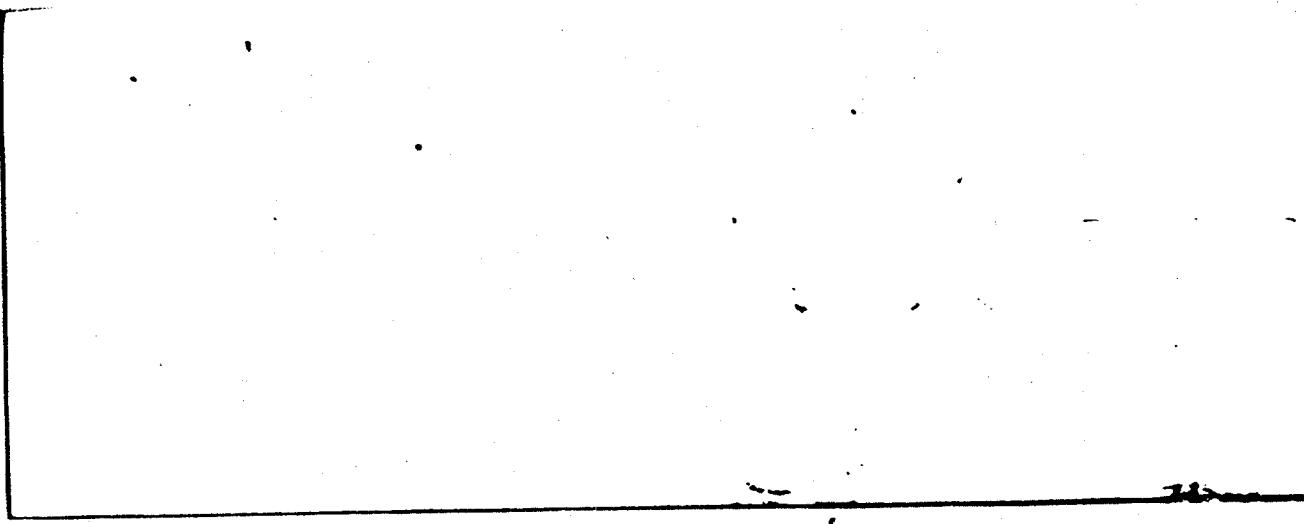
* Technical Error

PAGE 013

In compliance with the Good Laboratory Practice regulations, Study 9088 has been reviewed. The data presented in the final report accurately represents the data collected during the conduct of the study.

Dates of Inspection	Dates of reports to Management and Study Director
Jan. 14/80	Feb. 1/80
Jan. 21/80	March 3/80
Jan. 23/80	March 27/80
Jan. 28/80	April 28/80
Feb. 22/80	Sept. 5/80
Feb. 26/80	
Mar. 3/80	
Mar. 14/80	
Mar. 24/80	
Apr. 8/80	
Apr. 14/80	
Apr. 21/80	
June 28/80	
Sept. 5/80	

QUALITY ASSURANCE: D. Tozer DATE: Sept 9, 1980
D. Tozer



APPENDIX V
 (CONT'D.)

INDIVIDUAL BODY WEIGHTS (G)

FEMALES

GROUP NO.	RAT NO.	STUDY DAY						1.5
		-2.1	-1.1	0.1	0.3	0.5	1.1	
GROUP V								
COMPOUND BX-2487	551	119.0	126.0	139.0	138.0	137.0	144.0	147.0
2.5 MG/KG/DAY	552	107.0	121.0	132.0	133.0	134.0	138.0	141.0
553	111.0	124.0	137.0	139.0	136.0	145.0	146.0	
554	109.0	123.0	136.0	141.0	141.0	144.0	147.0	
555	122.0	132.0	147.0	149.0	151.0	156.0	158.0	156.0
GROUP VI								
COMPOUND BX-2487	651	117.0	129.0	139.0	144.0	144.0	145.0	149.0
50 MG/KG/DAY	652	98.0	113.0	123.0	125.0	125.0	129.0	132.0
653	120.0	132.0	144.0	149.0	148.0	151.0	152.0	154.0
654	109.0	118.0	133.0	139.0	138.0	140.0	143.0	145.0
655	103.0	117.0	133.0	133.0	134.0	137.0	141.0	146.0
GROUP VII								
COMPOUND BX-2326	751	109.0	124.0	136.0	136.0	140.0	142.0	147.0
50 MG/KG/DAY	752	105.0	120.0	133.0	134.0	139.0	141.0	143.0
753	117.0	132.0	144.0	149.0	145.0	149.0	153.0	
754	103.0	122.0	133.0	136.0	133.0	136.0	138.0	141.0
755	107.0	120.0	131.0	131.0	132.0	134.0	139.0	139.0

(CONTINUED)

APPENDIX V
(CONT'D.)

FEMALES

GROUP NO.	RAT NO.	STUDY DAY						
		2.1	2.3	2.5	3.1	4.1	5.1	6.1
GROUP V								
COMPOUND BX-2487	551	150.0	152.0	150.0	153.0	160.0	159.0	165.0
2.5 MG/KG/DAY	552	143.0	143.0	141.0	141.0	150.0	144.0	143.0
	553	149.0	150.0	149.0	152.0	154.0	154.0	146.0
	554	152.0	153.0	153.0	153.0	161.0	157.0	161.0
	555	163.0	165.0	165.0	167.0	175.0	174.0	163.0
GROUP VI								
COMPOUND BX-2487	651	151.0	153.0	153.0	157.0	164.0	165.0	167.0
5.0 MG/KG/DAY	652	136.0	138.0	141.0	144.0	147.0	150.0	152.0
	653	160.0	162.0	155.0	158.0	166.0	164.0	157.0
	654	144.0	149.0	150.0	140.0	146.0	146.0	149.0
	655	142.0	144.0	146.0	146.0	148.0	145.0	149.0
GROUP VII								
COMPOUND BX-2326	751	148.0	147.0	150.0	155.0	157.0	154.0	160.0
5.0 MG/KG/DAY	752	146.0	146.0	150.0	145.0	154.0	157.0	162.0
	753	157.0	159.0	161.0	160.0	164.0	165.0	168.0
	754	142.0	147.0	146.0	149.0	155.0	155.0	157.0
	755	142.0	141.0	139.0	144.0	146.0	148.0	155.0

- 101 -

(CONTINUED)

EXPERIMENTAL V
(CONT'D.)

INDIVIDUAL BODY WEIGHTS (G)

PENALIES

STUDY DAY

GROUP NO.

RAT NO. 8.1 9.1 10.1 11.1 12.1 13.1

GROUP V
CONFOUND BX-2467
2.5 MG/AC/DAY

551 170.0 170.0 171.0 173.0 174.0 163.0
552 145.0 150.0 150.0 158.0 162.0 146.0
553 159.0 162.0 164.0 164.0 166.0 148.0
554 160.0 162.0 165.0 164.0 167.0 157.0
555 175.0 185.0 189.0 186.0 191.0 179.0

GROUP VI
CONFOUND BX-2326
50 MG/AC/DAY

651 170.0 173.0 167.0 174.0 177.0 163.0
652 154.0 159.0 156.0 156.0 162.0 146.0
653 167.0 171.0 175.0 173.0 178.0 157.0
654 147.0 147.0 147.0 152.0 156.0 142.0
655 169.0 149.0 149.0 147.0 157.0 143.0
751 154.0 163.0 166.0 161.0 164.0 152.0
752 154.0 155.0 156.0 155.0 155.0 149.0
753 167.0 171.0 175.0 175.0 178.0 157.0
754 158.0 160.0 163.0 162.0 162.0 146.0
755 155.0 157.0 157.0 157.0 157.0 148.0

GROUP VII
CONFOUND BX-2326
50 MG/AC/DAY

163.0 163.0 163.0 163.0 163.0 148.0
160.0 160.0 163.0 162.0 162.0 146.0
167.0 167.0 167.0 167.0 167.0 148.0
171.0 171.0 175.0 175.0 178.0 157.0
175.0 175.0 175.0 175.0 178.0 157.0
179.0 179.0 179.0 179.0 179.0 157.0

APPENDIX VI

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/RAT/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)					
	-2.1	-1.1	0.1	1.1	2.1	
	TO	TO	TO	TO	TO	
RAT NO.	-1.1	0.1	1.1	2.1	3.1	
101	13.3	16.3	16.4	16.4	15.7	
102	14.3	15.6	15.3	14.3	13.3	
103	12.9	15.0	15.0	15.6	15.7	
104	16.3	18.7	17.3	17.1	15.9	
105	12.1	12.9	13.3	12.9	11.9	
201	12.9	15.1	15.1	14.6	13.7	
202	13.3	15.7	15.7	15.1	14.9	
203	13.6	16.1	15.0	14.1	13.7	
204	15.0	17.4	17.3	16.7	14.9	
205	16.0	18.7	18.1	17.7	16.6	
301	17.4	17.6	16.6	17.0	17.3	
302	14.0	15.9	16.0	15.9	15.0	
303	15.6	16.4	16.0	16.1	14.3	
304	14.7	16.9	16.4	17.1	15.3	
305	17.1	18.9	18.3	19.7	17.7	
401	14.7	15.7	14.6	13.1	12.3	
402	13.3	13.9	13.3	13.0	12.7	
403	13.9	14.9	12.3	11.9	11.4	
404	15.9	18.0	16.3	16.3	17.1	
405	15.7	16.1	14.0	13.4	14.0	

(CONTINUED)

APPENDIX VI
(CONT'D.)

INDIVIDUAL
ABSOLUTE FOOD CONSUMPTION (G/KAT/DAY)

MALES

GROUP NO.	STUDY INTERVAL (DAYS)		
	-2.1	-1.1	0.1
	TO TU	TO TU	TO TU
RAT NO.	-1.1	0.1	1.1
			2.1
			3.1
501	16.4	17.3	16.6
502	14.0	14.4	13.9
503	16.3	17.4	18.7
504	14.7	17.4	16.0
505	11.3	13.0	13.6
601	14.0	16.6	15.6
602	14.6	15.7	14.6
603	16.0	18.0	13.7
604	15.7	17.1	12.4
605	15.4	16.0	13.9
701	15.7	16.9	16.3
702	14.9	17.0	9.0
703	15.1	16.7	13.4
704	15.9	17.4	16.4
705	13.6	14.9	15.4
GROUP V COMPOUND BX-2487 2.5 MG/KG/DAY			
GROUP VI COMPOUND BX-2487 50 MG/KG/DAY			
GROUP VII COMPOUND BX-2326 50 MG/KG/DAY			

(CONTINUED)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Ronald L. Keener, Ph.D.
Regulatory Affairs Director, Product Integrity Department
Rohm and Haas Company
Independence Mall West
Philadelphia, Pennsylvania 19105

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAR 06 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

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U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan
Terry R. O'Bryan
Risk Analysis Branch

Enclosure

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Date sent to triage: MAY 05 1995

NON-CAP

CAP

Submission number: 12089 A

TSCA Inventory: Y N D

Study type (circle appropriate):

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Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

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STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

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Notes:

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~~B X 2475 was evaluated already.~~

Please evaluate the mixture B X-2326 and
the other compound B X 2487.

Thanks.

For Contractor Use Only

entire document: 0 1 2 pages 1

pages 1, tabs

Notes:

Contractor reviewer: LPS

Date: 12/22/94

INFORMATION REQUESTED: FLWP DATE:

TYPE: INT: SUPP FLWP

SUBMITTER NAME: Rohm and Haas Company

DISPOSITION:

0639 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

SUB DATE: 08/13/92 OTS DATE: 09/08/92 CSRAD DATE: 08/13/94

CHEMICAL NAME:

CAS#

110-26-9

VOLUNTARY ACTIONS:

0401 NO ACTION RI PORTED

0402 STUDIES PLANNED/INITIATED

0403 NOTIFICATION OF WORK ROUTINES

0404 LABEL/MSDS CHANGES

0405 PROCESS/HANDLING CHANGES

0406 APP/USE DISCONTINUED

0407 PRODUCTION DISCONTINUED

0408 CONFIDENTIAL

INFORMATION TYPE:

P F C

INFORMATION TYPE:

P F C

INFORMATION TYPE:

P F C

0201	ONCO (HUMAN)	01 02 04	0216	EPICLIN	01 02 04	0241	IMMUNO (ANIMAL)	01 02 04
0202	ONCO (ANIMAL)	01 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243	CHEM/PHYS PROP	01 02 04
0204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPROTERATO (HUMAN)	01 02 04	0221	ENV OCCURELFADE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
0207	REPROTERATO (ANIMAL)	01 02 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
0208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQUEST DELAY	01 02 04	0248	PROD/USE/PROC	01 02 04
0209	NEURO (ANIMAL)	01 02 04	0224	PRODCOMP/PCHEM ID	01 02 04	0251	MSDS	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	0259	OTHER	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04	0226	CONFIDENTIAL	01 02 04			
0212	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
0213	SUB ACUTE TOX (ANIMAL)	01 02 04	0228	ALLERG (ANIMAL)	01 02 04			
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
0215	CHRONIC TOX (ANIMAL)	01 02 04	0240	METAB/PHARMACO (HUMAN)	01 02 04			

TRIAGE DATE:

NON-CBI INVENTORY

ONGOING REVIEW

SPECIES

USE:

PRODUCTION:

TOXICOLOGICAL CONCERN:

P

F

C

CAS SR

YES

YES (DROP/REFER)

RAT

LOW

P

F

C

NO

NO (CONTINUE)

MED

P

F

C

DETERMINE

REFER:

HIGH

COMMENTS:

Rats were given i.v. pentobarbital injection & profenamide, N,N'-methylene bis produced. Neurotoxic effects including fits - toe walking, body tremors, piloerection and loss of limb use observed at all dose levels.

"12089A-02" = "L" = "FISCHER 344 RATS (5/SEX/DOSE) WERE GIVEN INTRAPERITONEAL INJECTIONS OF 2.5 OR 50 MG/KG BX-2487 (CAS NO.- UNKNOWN) ONCE DAILY, 5 DAYS/WEEK, FOR 13 WEEKS. NO MORTALITY OCCURRED. DECREASED BODY WEIGHT (MALES ONLY), REDUCED FOOD CONSUMPTION, SALIVATION, LACRIMATION, HUNCH-BACK POSITION, TIP-TOE WALKING, PILOERECTION, AND URINE STAINS OCCURRED IN RATS DOSED AT 50 MG/KG. STAINING AROUND THE EYES AND NOSE AND OCCASIONAL LACRIMATION AND BODY TREMORS OCCURRED IN RATS DOSED AT 2.5 MG/KG. EXTENSIVE PERIPHERAL NERVE DAMAGE IN THE FORM OF FIBER LOSS, MYELIN DISINTEGRATION, TOMACULUM AND OVOID FORMATION, AND OXONAL SWELLING OCCURRED; CHANGES SEEN IN HIGH DOSE RATS WERE LESS THAN THOSE SEEN IN LOW DOSE RATS. MEDULLA OBLONGATA FIBERS IN LOW DOSE MALES SHOWED DISINTEGRATION AND POSSIBLE OVOID FORMATION."

"12089A-03" = "FISCHER 344 RATS (5/SEX/DOSE) WERE GIVEN INTRAPERITONEAL INJECTIONS OF 50 MG/KG BX-2326 (CAS NO.- UNKNOWN; MIXTURE OF BX-2487 AND BX-2475) ONCE DAILY, 5 DAYS/WEEK, FOR 13 WEEKS. NO MORTALITY OCCURRED. SPORADIC LACRIMATION OCCURRED SHORTLY AFTER DOSING. MALES HAD SLIGHTLY LOWER BODY WEIGHT GAINS AND DECREASED FOOD CONSUMPTION. MODERATE TO SEVERE PERIPHERAL NERVE DAMAGE IN THE FORM OF FIBER LOSS, FOLDED OR CORRUGATED MYELIN, MYELIN DISINTEGRATION, TOMACULUM AND OVOID FORMATION, AND OXONAL SWELLING OCCURRED. MEDULLA OBLONGATA FIBERS SHOWED MINOR OR NO CHANGES."